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[ ] continuation patent application of
[ ] divisional patent application of
[X] continuation-in-part patent application of

Inventor(s)/Applicant Identifier: **John Fikes, Alessandro Sette, John Sidney, Scott Southwood, Robert Chesnut, Esteban Celis** and **Elissa Keogh**

For: **INDUCING CELLULAR IMMUNE RESPONSES TO HER2/neu USING PEPTIDE AND NUCLEIC ACID COMPOSITIONS**

[X] This application claims priority from each of the following Application Nos./filing dates:
09/189,702 filed November 10, 1998; 08/205,713 filed March 4, 1994; 08/159,184 filed November 29, 1993; 08/073,205 filed June 4, 1993 and 08/027,146 filed March 5, 1993,
the disclosure(s) of which is (are) incorporated by reference.
[ ] Please amend this application by adding the following before the first sentence: "This application is a [ ] continuation [ ] continuation-in-part of and claims the benefit of U.S. Application No. 60/_____, filed _____, the disclosure of which is incorporated by reference."

Enclosed are:
[X] 212 page(s) of specification
[X] 6 page(s) of claims
[X] 1 page of Abstract
[ ] _____ sheet(s) of [ ] formal [ ] informal drawing(s).
[ ] An assignment of the invention to _____
[X] A [ ] signed [ ] unsigned Declaration & Power of Attorney
[ ] A [ ] signed [ ] unsigned Declaration.
[ ] A Power of Attorney.
[ ] A verified statement to establish small entity status under 37 CFR 1.9 and 37 CFR 1.27 [ ] is enclosed [ ] was filed in the prior application and small entity status is still proper and desired.
[ ] A certified copy of a _____ application.
[ ] Information Disclosure Statement under 37 CFR 1.97.
[ ] A petition to extend time to respond in the parent application.
[ ] Notification of change of [ ] power of attorney [ ] correspondence address filed in prior application.
[ ]

In view of the Unsigned Declaration as filed with this application and pursuant to 37 CFR §1.53(f), Applicant requests deferral of the filing fee until submission of the Missing Parts of Application.

DO NOT CHARGE THE FILING FEE AT THIS TIME.

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PATENT APPLICATION

INDUCING CELLULAR IMMUNE RESPONSES TO HER2/neu USING PEPTIDE AND NUCLEIC ACID COMPOSITIONS

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PATENT

Attorney Docket No.: 018623-014800US

INDUCING CELLULAR IMMUNE RESPONSES TO HER2/neu USING PEPTIDE AND NUCLEIC ACID COMPOSITIONS

CROSS-REFERENCES TO RELATED APPLICATIONS

This application is a Continuation-In-Part ("CIP") of U.S.S.N. 09/189,702, filed 11/10/98, which is a CIP of U.S.S.N 08/205,713 filed 3/4/94, which is a CIP of abandoned U.S.S.N. 08/159,184 filed 11/29/93, which is a CIP of abandoned U.S.S.N. 08/073,205 filed 6/4/93 which is a CIP of abandoned U.S.S.N 08/027,146 filed 3/5/93. The present application is also related to U.S.S.N. 09/226,775, which is a CIP of abandoned U.S.S.N. 08/815,396, which claims benefit of abandoned U.S.S.N. 60/013,113. Furthermore, the present application is related to U.S.S.N. 09/017,735, which is a CIP of abandoned U.S.S.N. 08/589,108; U.S.S.N. 08/454,033; and U.S.S.N. 08/349,177. The present application is also related to U.S.S.N. 09/017,524, U.S.S.N. 08/821,739, which claims benefit of abandoned U.S.S.N. 60/013,833; and U.S.S.N. 08/347,610, which is a CIP of U.S.S.N. 08/159,339, which is a CIP of abandoned U.S.S.N. 08/103,396, which is a CIP of abandoned U.S.S.N. 08/027,746, which is a CIP of abandoned U.S.S.N. 07/926,666. The present application is also related to U.S.S.N. 09/017,743, which is a CIP of abandoned U.S.S.N. 08/590,298; and U.S.S.N. 08/452,843, which is a CIP of U.S.S.N. 08/344,824, which is a CIP of abandoned U.S.S.N. 08/278,634. .The present application is also related to PCT application 99/12066 filed 5/28/99 which claims benefit of provisional U.S.S.N. 60/087,192, and U.S.S.N. 09/009,953, which is a CIP of abandoned U.S.S.N. 60/036,713 and abandoned U.S.S.N. 60/037,432. In addition, the present application is related to U.S.S.N. 09/098,584, U.S.S.N. 09/239,043, U.S.S.N. 60/117,486, U.S.S.N. 09/350,401, and U.S.S.N. 09/357,737. In addition, the present application is related to U.S. Patent Application entitled "Inducing Cellular Immune Responses to Carcinoembryonic Antigen Using Peptide and Nucleic Acid Compositions", Attorney Docket No. 018623-014400, filed of even date herewith; U.S. Patent Application entitled "Inducing Cellular Immune Responses to p53 Using Peptide and Nucleic Acid Compositions", Attorney Docket No. 018623-014500, filed of even date herewith; and U.S. Patent Application entitled "Inducing Cellular Immune Responses to MAGE2/3 Using Peptide and Nucleic Acid Compositions", Attorney Docket No. 018623-

014600, filed of even date herewith. All of the above applications are incorporated herein by reference.

FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

This invention was funded, in part, by the United States government under grants with the National Institutes of Health. The U.S. government has certain rights in this invention.

INDEX

I. BACKGROUND OF THE INVENTION

A growing body of evidence suggests that cytotoxic T lymphocytes (CTL) are important in the immune response to tumor cells. CTL recognize peptide epitopes in the context of HLA class I molecules that are expressed on the surface of almost all nucleated cells. Following intracellular processing of endogenously synthesized tumor antigens, antigen-derived peptide epitopes bind to class I HLA molecules in the endoplasmic reticulum, and the resulting complex is then transported to the cell surface. CTL recognize the peptide-HLA class I complex, which then results in the destruction of the cell bearing the HLA-peptide complex directly by the CTL and/or via the activation of non-destructive mechanisms, *e.g.*, activation of lymphokines such as tumor necrosis factor-α (TNF- α) or interferon-γ (IFNγ) which enhance the immune response and facilitate the destruction of the tumor cell.

Tumor-specific helper T lymphocytes (HTLs) are also known to be important for maintaining effective antitumor immunity. Their role in antitumor immunity has been demonstrated in animal models in which these cells not only serve to provide help for induction of CTL and antibody responses, but also provide effector functions, which are mediated by direct cell contact and also by secretion of lymphokines (*e.g.*, IFNγ and TNF- α).

A fundamental challenge in the development of an efficacious tumor vaccine is immune suppression or tolerance that can occur. There is therefore a need to establish vaccine embodiments that elicit immune responses of sufficient breadth and vigor to prevent progression and/or clear the tumor.

The epitope approach, as we have described, may represent a solution to this challenge, in that it allows the incorporation of various antibody, CTL and HTL epitopes, from discrete regions of a target TAA, and/or regions of other TAAs, in a single vaccine composition. Such a composition may simultaneously target multiple dominant and subdominant epitopes and thereby be used to achieve effective immunization in a diverse population.

HER2/neu (or erbB-2) is a 185 kD transmembrane protein with tyrosine kinase activity that has a structure similar to the epidermal growth factor receptor (Coussens et al., Science 230:113-119, 1985; Bargmann et al., Nature 319:226-230, 1986; Yamamoto et al., Nature 319:230-234, 1986). Amplification of the Her2/neu gene and/or overexpression of the protein have been reported in many human adenocarcinomas of the

breast, ovary, uterus, prostate, stomach, esophagus, pancreas, kidney, and lung (*see, e.g.*, Slamon *et al.*, *Science* 235:177-182, 1987 and *Science* 244:707-712, 1989; Borg *et al.*, *Cancer Res.* 50:4332-4337, 1990; Lukes *et al.*, *Cancer* 73:2380-2385, 1994; Kuhn *et al.*, *J. Urol.* 150:1427-1433, 1993; Sadasivan *et al.*, *J. Urol.* 150:126-131, 1993; Yonemura *et al.*, *Cancer Res.* 51:1034-1038, 1991; Kameda *et al.*, *Cancer Res.* 50:8002-8009, 1990; Houldsworth *et al.*, Cancer Res. 50:6417-6422, 1990; Yamanaka *et al.*, *Human Path.* 24:1127-1134, 1993; Weidner *et al.*, *Cancer Res.* 50:4504-4509, 1990; Kern *et al.*, *Cancer Res.* 50:5184-5187, 1990; and Rachwal *et al.*, *Br. J. Cancer* 72:56-64, 1995). This widespread expression on cancer cells makes HER2/neu an important target for immunotherapy.

The information provided in this section is intended to disclose the presently understood state of the art as of the filing date of the present application. Information is included in this section which was generated subsequent to the priority date of this application. Accordingly, information in this section is not intended, in any way, to delineate the priority date for the invention.

II. SUMMARY OF THE INVENTION

This invention applies our knowledge of the mechanisms by which antigen is recognized by T cells, for example, to develop epitope-based vaccines directed towards TAAs. More specifically, this application communicates our discovery of specific epitope pharmaceutical compositions and methods of use in the prevention and treatment of cancer.

Upon development of appropriate technology, the use of epitope-based vaccines has several advantages over current vaccines, particularly when compared to the use of whole antigens in vaccine compositions. For example, immunosuppressive epitopes that may be present in whole antigens can be avoided with the use of epitope-based vaccines. Such immunosuppressive epitopes may, *e.g.*, correspond to immunodominant epitopes in whole antigens, which may be avoided by selecting peptide epitopes from non-dominant regions (*see, e.g.*, Disis *et al.*, *J. Immunol.* 156:3151-3158, 1996).

An additional advantage of an epitope-based vaccine approach is the ability to combine selected epitopes (CTL and HTL), and further, to modify the composition of the epitopes, achieving, for example, enhanced immunogenicity. Accordingly, the immune response can be modulated, as appropriate, for the target disease. Similar engineering of the response is not possible with traditional approaches.

Another major benefit of epitope-based immune-stimulating vaccines is their safety. The possible pathological side effects caused by infectious agents or whole protein antigens, which might have their own intrinsic biological activity, is eliminated.

An epitope-based vaccine also provides the ability to direct and focus an immune response to multiple selected antigens from the same pathogen (a "pathogen" may be an infectious agent or a tumor-associated molecule). Thus, patient-by-patient variability in the immune response to a particular pathogen may be alleviated by inclusion of epitopes from multiple antigens from the pathogen in a vaccine composition.

Furthermore, an epitope-based anti-tumor vaccine also provides the opportunity to combine epitopes derived from multiple tumor-associated molecules. This capability can therefore address the problem of tumor-to tumor variability that arises when developing a broadly targeted anti-tumor vaccine for a given tumor type and can also reduce the likelihood of tumor escape due to antigen loss. For example, a breast cancer tumor in one patient may express a target TAA that differs from a breast cancer tumor in another patient. Epitopes derived from multiple TAAs can be included in a polyepitopic vaccine that will target both breast cancer tumors.

One of the most formidable obstacles to the development of broadly efficacious epitope-based immunotherapeutics, however, has been the extreme polymorphism of HLA molecules. To date, effective non-genetically biased coverage of a population has been a task of considerable complexity; such coverage has required that epitopes be used that are specific for HLA molecules corresponding to each individual HLA allele. Impractically large numbers of epitopes would therefore have to be used in order to cover ethnically diverse populations. Thus, there has existed a need for peptide epitopes that are bound by multiple HLA antigen molecules for use in epitope-based vaccines. The greater the number of HLA antigen molecules bound, the greater the breadth of population coverage by the vaccine.

Furthermore, as described herein in greater detail, a need has existed to modulate peptide binding properties, *e.g.*, so that peptides that are able to bind to multiple HLA molecules do so with an affinity that will stimulate an immune response. Identification of epitopes restricted by more than one HLA allele at an affinity that correlates with immunogenicity is important to provide thorough population coverage, and to allow the elicitation of responses of sufficient vigor to prevent or clear an infection in a diverse segment of the population. Such a response can also target a broad array of epitopes. The technology disclosed herein provides for such favored immune responses.

In a preferred embodiment, epitopes for inclusion in vaccine compositions of the invention are selected by a process whereby protein sequences of known antigens are evaluated for the presence of motif or supermotif-bearing epitopes. Peptides corresponding to a motif- or supermotif-bearing epitope are then synthesized and tested for the ability to bind to the HLA molecule that recognizes the selected motif. Those peptides that bind at an intermediate or high affinity *i.e.*, an IC_{50} (or a K_D value) of 500 nM or less for HLA class I molecules or an IC_{50} of 1000 nM or less for HLA class II molecules, are further evaluated for their ability to induce a CTL or HTL response. Immunogenic peptide epitopes are selected for inclusion in vaccine compositions.

Supermotif-bearing peptides may additionally be tested for the ability to bind to multiple alleles within the HLA supertype family. Moreover, peptide epitopes may be analogued to modify binding affinity and/or the ability to bind to multiple alleles within an HLA supertype.

The invention also includes embodiments comprising methods for monitoring or evaluating an immune response to a TAA in a patient having a known HLA-type. Such methods comprise incubating a T lymphocyte sample from the patient with a peptide composition comprising a TAA epitope that has an amino acid sequence described in Tables VII to Table XX or Table XXII which binds the product of at least one HLA allele present in the patient, and detecting for the presence of a T lymphocyte that binds to the peptide. A CTL peptide epitope may, for example, be used as a component of a tetrameric complex for this type of analysis.

An alternative modality for defining the peptide epitopes in accordance with the invention is to recite the physical properties, such as length; primary structure; or charge, which are correlated with binding to a particular allele-specific HLA molecule or group of allele-specific HLA molecules. A further modality for defining peptide epitopes is to recite the physical properties of an HLA binding pocket, or properties shared by several allele-specific HLA binding pockets (*e.g.* pocket configuration and charge distribution) and reciting that the peptide epitope fits and binds to the pocket or pockets.

As will be apparent from the discussion below, other methods and embodiments are also contemplated. Further, novel synthetic peptides produced by any of the methods described herein are also part of the invention.

III. BRIEF DESCRIPTION OF THE FIGURES

not applicable

IV. DETAILED DESCRIPTION OF THE INVENTION

The peptide epitopes and corresponding nucleic acid compositions of the present invention are useful for stimulating an immune response to a TAA by stimulating the production of CTL or HTL responses. The peptide epitopes, which are derived directly or indirectly from native TAA protein amino acid sequences, are able to bind to HLA molecules and stimulate an immune response to the TAA. The complete sequence of the TAA proteins to be analyzed can be obtained from GenBank. Peptide epitopes and analogs thereof can also be readily determined from sequence information that may subsequently be discovered for heretofore unknown variants of particular TAAs, as will be clear from the disclosure provided below.

A list of target TAA includes, but is not limited to, the following antigens: MAGE 1, MAGE 2, MAGE 3, MAGE-11, MAGE-A10, BAGE, GAGE, RAGE, MAGE-C1, LAGE-1, CAG-3, DAM, MUC1, MUC2, MUC18, NY-ESO-1, MUM-1, CDK4, BRCA2, NY-LU-1, NY-LU-7, NY-LU-12, CASP8, RAS, KIAA-2-5, SCCs, p53, p73, CEA, Her 2/neu, Melan-A, gp100, tyrosinase, TRP2, gp75/TRP1, kallikrein, PSM, PAP, PSA, PT1-1, B-catenin, PRAME, Telomerase, FAK, cyclin D1 protein, NOEY2, EGF-R, SART-1, CAPB, HPVE7, p15, Folate receptor CDC27, PAGE-1, and PAGE-4.

The peptide epitopes of the invention have been identified in a number of ways, as will be discussed below. Also discussed in greater detail is that analog peptides have been derived and the binding activity for HLA molecules modulated by modifying specific amino acid residues to create peptide analogs exhibiting altered immunogenicity. Further, the present invention provides compositions and combinations of compositions that enable epitope-based vaccines that are capable of interacting with HLA molecules encoded by various genetic alleles to provide broader population coverage than prior vaccines.

IV.A. Definitions

The invention can be better understood with reference to the following definitions, which are listed alphabetically:

A "computer" or "computer system" generally includes: a processor; at least one information storage/retrieval apparatus such as, for example, a hard drive, a disk drive or a tape drive; at least one input apparatus such as, for example, a keyboard, a mouse, a touch screen, or a microphone; and display structure. Additionally, the computer may

include a communication channel in communication with a network. Such a computer may include more or less than what is listed above.

"Cross-reactive binding" indicates that a peptide is bound by more than one HLA molecule; a synonym is degenerate binding.

A "cryptic epitope" elicits a response by immunization with an isolated peptide, but the response is not cross-reactive *in vitro* when intact whole protein which comprises the epitope is used as an antigen.

A "dominant epitope" is an epitope that induces an immune response upon immunization with a whole native antigen (see, *e.g.*, Sercarz, *et al.*, *Annu. Rev. Immunol.* 11:729-766, 1993). Such a response is cross-reactive *in vitro* with an isolated peptide epitope.

With regard to a particular amino acid sequence, an "epitope" is a set of amino acid residues which is involved in recognition by a particular immunoglobulin, or in the context of T cells, those residues necessary for recognition by T cell receptor proteins and/or Major Histocompatibility Complex (MHC) receptors. In an immune system setting, *in vivo* or *in vitro*, an epitope is the collective features of a molecule, such as primary, secondary and tertiary peptide structure, and charge, that together form a site recognized by an immunoglobulin, T cell receptor or HLA molecule. Throughout this disclosure epitope and peptide are often used interchangeably. It is to be appreciated, however, that isolated or purified protein or peptide molecules larger than and comprising an epitope of the invention are still within the bounds of the invention.

"Human Leukocyte Antigen" or "HLA" is a human class I or class II Major Histocompatibility Complex (MHC) protein (*see*, *e.g.*, Stites, *et al.*, IMMUNOLOGY, 8TH ED., Lange Publishing, Los Altos, CA, 1994).

An "HLA supertype or family", as used herein, describes sets of HLA molecules grouped on the basis of shared peptide-binding specificities. HLA class I molecules that share somewhat similar binding affinity for peptides bearing certain amino acid motifs are grouped into HLA supertypes. The terms HLA superfamily, HLA supertype family, HLA family, and HLA xx-like molecules (where xx denotes a particular HLA type), are synonyms.

Throughout this disclosure, results are expressed in terms of "IC_{50}'s." IC_{50} is the concentration of peptide in a binding assay at which 50% inhibition of binding of a reference peptide is observed. Given the conditions in which the assays are run (*i.e.*, limiting HLA proteins and labeled peptide concentrations), these values approximate K_D

values. Assays for determining binding are described in detail, *e.g.*, in PCT publications WO 94/20127 and WO 94/03205. It should be noted that IC_{50} values can change, often dramatically, if the assay conditions are varied, and depending on the particular reagents used (*e.g.*, HLA preparation, *etc.*). For example, excessive concentrations of HLA molecules will increase the apparent measured IC_{50} of a given ligand.

Alternatively, binding is expressed relative to a reference peptide. Although as a particular assay becomes more, or less, sensitive, the IC_{50}'s of the peptides tested may change somewhat, the binding relative to the reference peptide will not significantly change. For example, in an assay run under conditions such that the IC_{50} of the reference peptide increases 10-fold, the IC_{50} values of the test peptides will also shift approximately 10-fold. Therefore, to avoid ambiguities, the assessment of whether a peptide is a good, intermediate, weak, or negative binder is generally based on its IC_{50}, relative to the IC_{50} of a standard peptide.

Binding may also be determined using other assay systems including those using: live cells (*e.g.*, Ceppellini *et al.*, *Nature* 339:392, 1989; Christnick *et al.*, *Nature* 352:67, 1991; Busch *et al.*, *Int. Immunol.* 2:443, 19990; Hill *et al.*, *J. Immunol.* 147:189, 1991; del Guercio *et al.*, *J. Immunol.* 154:685, 1995), cell free systems using detergent lysates (*e.g.*, Cerundolo *et al.*, *J. Immunol.* 21:2069, 1991), immobilized purified MHC (*e.g.*, Hill *et al.*, *J. Immunol.* 152, 2890, 1994; Marshall *et al.*, *J. Immunol.* 152:4946, 1994), ELISA systems (*e.g.*, Reay *et al.*, *EMBO J.* 11:2829, 1992), surface plasmon resonance (*e.g.*, Khilko *et al.*, *J. Biol. Chem.* 268:15425, 1993); high flux soluble phase assays (Hammer *et al.*, *J. Exp. Med.* 180:2353, 1994), and measurement of class I MHC stabilization or assembly (*e.g.*, Ljunggren *et al.*, *Nature* 346:476, 1990; Schumacher *et al.*, *Cell* 62:563, 1990; Townsend *et al.*, *Cell* 62:285, 1990; Parker *et al.*, *J. Immunol.* 149:1896, 1992).

As used herein, "high affinity" with respect to HLA class I molecules is defined as binding with an IC_{50}, or K_D value, of 50 nM or less; "intermediate affinity" is binding with an IC_{50} or K_D value of between about 50 and about 500 nM. "High affinity" with respect to binding to HLA class II molecules is defined as binding with an IC_{50} or K_D value of 100 nM or less; "intermediate affinity" is binding with an IC_{50} or K_D value of between about 100 and about 1000 nM.

The terms "identical" or percent "identity," in the context of two or more peptide sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues that are the same, when compared and

aligned for maximum correspondence over a comparison window, as measured using a sequence comparison algorithm or by manual alignment and visual inspection.

An "immunogenic peptide" or "peptide epitope" is a peptide that comprises an allele-specific motif or supermotif such that the peptide will bind an HLA molecule and induce a CTL and/or HTL response. Thus, immunogenic peptides of the invention are capable of binding to an appropriate HLA molecule and thereafter inducing a cytotoxic T cell response, or a helper T cell response, to the antigen from which the immunogenic peptide is derived.

The phrases "isolated" or "biologically pure" refer to material which is substantially or essentially free from components which normally accompany the material as it is found in its native state. Thus, isolated peptides in accordance with the invention preferably do not contain materials normally associated with the peptides in their *in situ* environment.

"Major Histocompatibility Complex" or "MHC" is a cluster of genes that plays a role in control of the cellular interactions responsible for physiologic immune responses. In humans, the MHC complex is also known as the HLA complex. For a detailed description of the MHC and HLA complexes, see, Paul, FUNDAMENTAL IMMUNOLOGY, 3RD ED., Raven Press, New York, 1993.

The term "motif" refers to the pattern of residues in a peptide of defined length, usually a peptide of from about 8 to about 13 amino acids for a class I HLA motif and from about 6 to about 25 amino acids for a class II HLA motif, which is recognized by a particular HLA molecule. Peptide motifs are typically different for each protein encoded by each human HLA allele and differ in the pattern of the primary and secondary anchor residues.

A "negative binding residue" or "deleterious residue" is an amino acid which, if present at certain positions (typically not primary anchor positions) in a peptide epitope, results in decreased binding affinity of the peptide for the peptide's corresponding HLA molecule.

The term "peptide" is used interchangeably with "oligopeptide" in the present specification to designate a series of residues, typically L-amino acids, connected one to the other, typically by peptide bonds between the α-amino and carboxyl groups of adjacent amino acids. The preferred CTL-inducing peptides of the invention are 13 residues or less in length and usually consist of between about 8 and about 11 residues, preferably 9 or 10 residues. The preferred HTL-inducing oligopeptides are less than

about 50 residues in length and usually consist of between about 6 and about 30 residues, more usually between about 12 and 25, and often between about 15 and 20 residues.

"Pharmaceutically acceptable" refers to a non-toxic, inert, and/or physiologically compatible composition.

A "primary anchor residue" is an amino acid at a specific position along a peptide sequence which is understood to provide a contact point between the immunogenic peptide and the HLA molecule. One to three, usually two, primary anchor residues within a peptide of defined length generally defines a "motif" for an immunogenic peptide. These residues are understood to fit in close contact with peptide binding grooves of an HLA molecule, with their side chains buried in specific pockets of the binding grooves themselves. In one embodiment, for example, the primary anchor residues are located at position 2 (from the amino terminal position) and at the carboxyl terminal position of a 9-residue peptide epitope in accordance with the invention. The primary anchor positions for each motif and supermotif are set forth in Table 1. For example, analog peptides can be created by altering the presence or absence of particular residues in these primary anchor positions. Such analogs are used to modulate the binding affinity of a peptide comprising a particular motif or supermotif.

"Promiscuous recognition" is where a distinct peptide is recognized by the same T cell clone in the context of various HLA molecules. Promiscuous recognition or binding is synonymous with cross-reactive binding.

A "protective immune response" or "therapeutic immune response" refers to a CTL and/or an HTL response to an antigen derived from an infectious agent or a tumor antigen, which prevents or at least partially arrests disease symptoms or progression. The immune response may also include an antibody response which has been facilitated by the stimulation of helper T cells.

The term "residue" refers to an amino acid or amino acid mimetic incorporated into an oligopeptide by an amide bond or amide bond mimetic.

A "secondary anchor residue" is an amino acid at a position other than a primary anchor position in a peptide which may influence peptide binding. A secondary anchor residue occurs at a significantly higher frequency amongst bound peptides than would be expected by random distribution of amino acids at one position. The secondary anchor residues are said to occur at "secondary anchor positions." A secondary anchor residue can be identified as a residue which is present at a higher frequency among high or intermediate affinity binding peptides, or a residue otherwise associated with high or

intermediate affinity binding. For example, analog peptides can be created by altering the presence or absence of particular residues in these secondary anchor positions. Such analogs are used to finely modulate the binding affinity of a peptide comprising a particular motif or supermotif.

A "subdominant epitope" is an epitope which evokes little or no response upon immunization with whole antigens which comprise the epitope, but for which a response can be obtained by immunization with an isolated peptide, and this response (unlike the case of cryptic epitopes) is detected when whole protein is used to recall the response *in vitro* or *in vivo*.

A "supermotif" is a peptide binding specificity shared by HLA molecules encoded by two or more HLA alleles. Preferably, a supermotif-bearing peptide is recognized with high or intermediate affinity (as defined herein) by two or more HLA molecules.

"Synthetic peptide" refers to a peptide that is not naturally occurring, but is man-made using such methods as chemical synthesis or recombinant DNA technology.

The nomenclature used to describe peptide compounds follows the conventional practice wherein the amino group is presented to the left (the N-terminus) and the carboxyl group to the right (the C-terminus) of each amino acid residue. When amino acid residue positions are referred to in a peptide epitope they are numbered in an amino to carboxyl direction with position one being the position closest to the amino terminal end of the epitope, or the peptide or protein of which it may be a part. In the formulae representing selected specific embodiments of the present invention, the amino- and carboxyl-terminal groups, although not specifically shown, are in the form they would assume at physiologic pH values, unless otherwise specified. In the amino acid structure formulae, each residue is generally represented by standard three letter or single letter designations. The L-form of an amino acid residue is represented by a capital single letter or a capital first letter of a three-letter symbol, and the D-form for those amino acids having D-forms is represented by a lower case single letter or a lower case three letter symbol. Glycine has no asymmetric carbon atom and is simply referred to as "Gly" or G. Symbols for the amino acids are shown below.

Single Letter Symbol	Three Letter Symbol	Amino Acids
A	Ala	Alanine
C	Cys	Cysteine
D	Asp	Aspartic Acid
E	Glu	Glutamic Acid
F	Phe	Phenylalanine
G	Gly	Glycine
H	His	Histidine
I	Ile	Isoleucine
K	Lys	Lysine
L	Leu	Leucine
M	Met	Methionine
N	Asn	Asparagine
P	Pro	Proline
Q	Gln	Glutamine
R	Arg	Arginine
S	Ser	Serine
T	Thr	Threonine
V	Val	Valine
W	Trp	Tryptophan
Y	Tyr	Tyrosine

IV.B. Stimulation of CTL and HTL responses

The mechanism by which T cells recognize antigens has been delineated during the past ten years. Based on our understanding of the immune system we have developed efficacious peptide epitope vaccine compositions that can induce a therapeutic or prophylactic immune response to a TAA in a broad population. For an understanding of the value and efficacy of the claimed compositions, a brief review of immunology-related technology is provided.

A complex of an HLA molecule and a peptidic antigen acts as the ligand recognized by HLA-restricted T cells (Buus, S. *et al.*, *Cell* 47:1071, 1986; Babbitt, B. P. *et al.*, *Nature* 317:359, 1985; Townsend, A. and Bodmer, H., *Annu. Rev. Immunol.* 7:601,

1989; Germain, R. N., *Annu. Rev. Immunol.* 11:403, 1993). Through the study of single amino acid substituted antigen analogs and the sequencing of endogenously bound, naturally processed peptides, critical residues that correspond to motifs required for specific binding to HLA antigen molecules have been identified and are described herein and are set forth in Tables I, II, and III (*see* also, *e.g.*, Southwood, *et al.*, *J. Immunol.* 160:3363, 1998; Rammensee, *et al.*, *Immunogenetics* 41:178, 1995; Rammensee *et al.*, SYFPEITHI, access via web at : http://134.2.96.221/scripts.hlaserver.dll/home.htm; Sette, A. and Sidney, J. *Curr. Opin. Immunol.* 10:478, 1998; Engelhard, V. H., *Curr. Opin. Immunol.* 6:13, 1994; Sette, A. and Grey, H. M., *Curr. Opin. Immunol.* 4:79, 1992; Sinigaglia, F. and Hammer, J. *Curr. Biol.* 6:52, 1994; Ruppert *et al.*, *Cell* 74:929-937, 1993; Kondo *et al.*, *J. Immunol.* 155:4307-4312, 1995; Sidney *et al.*, *J. Immunol.* 157:3480-3490, 1996; Sidney *et al.*, *Human Immunol.* 45:79-93, 1996; Sette, A. and Sidney, J. *Immunogenetics*, in press, 1999).

Furthermore, x-ray crystallographic analysis of HLA-peptide complexes has revealed pockets within the peptide binding cleft of HLA molecules which accommodate, in an allele-specific mode, residues borne by peptide ligands; these residues in turn determine the HLA binding capacity of the peptides in which they are present. (*See, e.g.*, Madden, D.R. *Annu. Rev. Immunol.* 13:587, 1995; Smith, *et al.*, *Immunity* 4:203, 1996; Fremont *et al.*, *Immunity* 8:305, 1998; Stern *et al.*, *Structure* 2:245, 1994; Jones, E.Y. *Curr. Opin. Immunol.* 9:75, 1997; Brown, J. H. *et al.*, *Nature* 364:33, 1993; Guo, H. C. *et al.*, *Proc. Natl. Acad. Sci. USA* 90:8053, 1993; Guo, H. C. *et al.*, *Nature* 360:364, 1992; Silver, M. L. *et al.*, *Nature* 360:367, 1992; Matsumura, M. *et al.*, *Science* 257:927, 1992; Madden *et al.*, *Cell* 70:1035, 1992; Fremont, D. H. *et al.*, *Science* 257:919, 1992; Saper, M. A. , Bjorkman, P. J. and Wiley, D. C., *J. Mol. Biol.* 219:277, 1991.)

Accordingly, the definition of class I and class II allele-specific HLA binding motifs, or class I or class II supermotifs allows identification of regions within a protein that have the potential of binding particular HLA molecules.

The present inventors have found that the correlation of binding affinity with immunogenicity, which is disclosed herein, is an important factor to be considered when evaluating candidate peptides. Thus, by a combination of motif searches and HLA-peptide binding assays, candidates for epitope-based vaccines have been identified. After determining their binding affinity, additional confirmatory work can be performed to select, amongst these vaccine candidates, epitopes with preferred characteristics in terms of population coverage, antigenicity, and immunogenicity.

Various strategies can be utilized to evaluate immunogenicity, including:

1) Evaluation of primary T cell cultures from normal individuals (*see, e.g.*, Wentworth, P. A. *et al.*, *Mol. Immunol.* 32:603, 1995; Celis, E. *et al.*, *Proc. Natl. Acad. Sci. USA* 91:2105, 1994; Tsai, V. *et al.*, *J. Immunol.* 158:1796, 1997; Kawashima, I. *et al.*, *Human Immunol.* 59:1, 1998); This procedure involves the stimulation of peripheral blood lymphocytes (PBL) from normal subjects with a test peptide in the presence of antigen presenting cells *in vitro* over a period of several weeks. T cells specific for the peptide become activated during this time and are detected using, *e.g.*, a ^{51}Cr-release assay involving peptide sensitized target cells.

2) Immunization of HLA transgenic mice (*see, e.g.*, Wentworth, P. A. *et al.*, *J. Immunol.* 26:97, 1996; Wentworth, P. A. *et al.*, *Int. Immunol.* 8:651, 1996; Alexander, J. *et al.*, *J. Immunol.* 159:4753, 1997); In this method, peptides in incomplete Freund's adjuvant are administered subcutaneously to HLA transgenic mice. Several weeks following immunization, splenocytes are removed and cultured *in vitro* in the presence of test peptide for approximately one week. Peptide-specific T cells are detected using, *e.g.*, a ^{51}Cr-release assay involving peptide sensitized target cells and target cells expressing endogenously generated antigen.

3) Demonstration of recall T cell responses from patients who have been effectively vaccinated or who have a tumor; (*see, e.g.*, Rehermann, B. *et al.*, *J. Exp. Med.* 181:1047, 1995; Doolan, D. L. *et al.*, *Immunity* 7:97, 1997; Bertoni, R. *et al.*, *J. Clin. Invest.* 100:503, 1997; Threlkeld, S. C. *et al.*, *J. Immunol.* 159:1648, 1997; Diepolder, H. M. *et al.*, *J. Virol.* 71:6011, 1997; Tsang *et al.*, *J. Natl. Cancer Inst.* 87:982-990, 1995; Disis *et al.*, *J. Immunol.* 156:3151-3158, 1996). In applying this strategy, recall responses are detected by culturing PBL from patients with cancer who have generated an immune response "naturally", or from patients who were vaccinated with tumor antigen vaccines. PBL from subjects are cultured *in vitro* for 1-2 weeks in the presence of test peptide plus antigen presenting cells (APC) to allow activation of "memory" T cells, as compared to "naive" T cells. At the end of the culture period, T cell activity is detected using assays for T cell activity including ^{51}Cr release involving peptide-sensitized targets, T cell proliferation, or lymphokine release.

The following describes the peptide epitopes and corresponding nucleic acids of the invention.

IV.C. Binding Affinity of Peptide Epitopes for HLA Molecules

As indicated herein, the large degree of HLA polymorphism is an important factor to be taken into account with the epitope-based approach to vaccine development. To address this factor, epitope selection encompassing identification of peptides capable of binding at high or intermediate affinity to multiple HLA molecules is preferably utilized, most preferably these epitopes bind at high or intermediate affinity to two or more allele-specific HLA molecules.

CTL-inducing peptides of interest for vaccine compositions preferably include those that have an IC_{50} or binding affinity value for class I HLA molecules of 500 nM or better (*i.e.*, the value is ≤ 500 nM). HTL-inducing peptides preferably include those that have an IC_{50} or binding affinity value for class II HLA molecules of 1000 nM or better, (*i.e.*, the value is ≤ 1,000 nM). For example, peptide binding is assessed by testing the capacity of a candidate peptide to bind to a purified HLA molecule *in vitro*. Peptides exhibiting high or intermediate affinity are then considered for further analysis. Selected peptides are tested on other members of the supertype family. In preferred embodiments, peptides that exhibit cross-reactive binding are then used in cellular screening analyses or vaccines.

As disclosed herein, higher HLA binding affinity is correlated with greater immunogenicity. Greater immunogenicity can be manifested in several different ways. Immunogenicity corresponds to whether an immune response is elicited at all, and to the vigor of any particular response, as well as to the extent of a population in which a response is elicited. For example, a peptide might elicit an immune response in a diverse array of the population, yet in no instance produce a vigorous response. Moreover, higher binding affinity peptides lead to more vigorous immunogenic responses. As a result, less peptide is required to elicit a similar biological effect if a high or intermediate affinity binding peptide is used. Thus, in preferred embodiments of the invention, high or intermediate affinity binding epitopes are particularly useful.

The relationship between binding affinity for HLA class I molecules and immunogenicity of discrete peptide epitopes on bound antigens has been determined for the first time in the art by the present inventors. The correlation between binding affinity and immunogenicity was analyzed in two different experimental approaches (*see, e.g.*, Sette, *et al., J. Immunol.* 153:5586-5592, 1994). In the first approach, the immunogenicity of potential epitopes ranging in HLA binding affinity over a 10,000-fold

range was analyzed in HLA-A*0201 transgenic mice. In the second approach, the antigenicity of approximately 100 different hepatitis B virus (HBV)-derived potential epitopes, all carrying A*0201 binding motifs, was assessed by using PBL from acute hepatitis patients. Pursuant to these approaches, it was determined that an affinity threshold value of approximately 500 nM (preferably 50 nM or less) determines the capacity of a peptide epitope to elicit a CTL response. These data are true for class I binding affinity measurements for naturally processed peptides and for synthesized T cell epitopes. These data also indicate the important role of determinant selection in the shaping of T cell responses (*see, e.g.,* Schaeffer *et al., Proc. Natl. Acad. Sci. USA* 86:4649-4653, 1989).

An affinity threshold associated with immunogenicity in the context of HLA class II DR molecules has also been delineated (*see, e.g.*, Southwood *et al. J. Immunology* 160:3363-3373,1998, and co-pending U.S.S.N. 09/009,953 filed 1/21/98). In order to define a biologically significant threshold of DR binding affinity, a database of the binding affinities of 32 DR-restricted epitopes for their restricting element (*i.e.*, the HLA molecule that binds the motif) was compiled. In approximately half of the cases (15 of 32 epitopes), DR restriction was associated with high binding affinities, *i.e.* binding affinity values of 100 nM or less. In the other half of the cases (16 of 32), DR restriction was associated with intermediate affinity (binding affinity values in the 100-1000 nM range). In only one of 32 cases was DR restriction associated with an IC_{50} of 1000 nM or greater. Thus, 1000 nM can be defined as an affinity threshold associated with immunogenicity in the context of DR molecules.

In the case of tumor-associated antigens, many CTL peptide epitopes that have been shown to induce CTL that lyse peptide-pulsed target cells and tumor cell targets endogenously expressing the epitope exhibit binding affinity or IC_{50} values of 200 nM or less. In a study that evaluated the association of binding affinity and immunogenicity of such TAA epitopes, 100% (10/10) of the high binders, *i.e.*, peptide epitopes binding at an affinity of 50 nM or less, were immunogenic and 80% (8/10) of them elicited CTLs that specifically recognized tumor cells. In the 51 to 200 nM range, very similar figures were obtained. CTL inductions positive for peptide and tumor cells were noted for 86% (6/7) and 71% (5/7) of the peptides, respectively. In the 201-500 nM range, most peptides (4/5 wildtype) were positive for induction of CTL recognizing wildtype peptide, but tumor recognition was not detected.

The binding affinity of peptides for HLA molecules can be determined as described in Example 1, below.

IV.D. Peptide Epitope Binding Motifs and Supermotifs

Through the study of single amino acid substituted antigen analogs and the sequencing of endogenously bound, naturally processed peptides, critical residues required for allele-specific binding to HLA molecules have been identified. The presence of these residues correlates with binding affinity for HLA molecules. The identification of motifs and/or supermotifs that correlate with high and intermediate affinity binding is an important issue with respect to the identification of immunogenic peptide epitopes for the inclusion in a vaccine. Kast *et al.* (*J. Immunol.* 152:3904-3912, 1994) have shown that motif-bearing peptides account for 90% of the epitopes that bind to allele-specific HLA class I molecules. In this study all possible peptides of 9 amino acids in length and overlapping by eight amino acids (240 peptides), which cover the entire sequence of the E6 and E7 proteins of human papillomavirus type 16, were evaluated for binding to five allele-specific HLA molecules that are expressed at high frequency among different ethnic groups. This unbiased set of peptides allowed an evaluation of the predictive value of HLA class I motifs. From the set of 240 peptides, 22 peptides were identified that bound to an allele-specific HLA molecule with high or intermediate affinity. Of these 22 peptides, 20 (*i.e.* 91%) were motif-bearing. Thus, this study demonstrates the value of motifs for the identification of peptide epitopes for inclusion in a vaccine: application of motif-based identification techniques will identify about 90% of the potential epitopes in a target antigen protein sequence.

Such peptide epitopes are identified in the Tables described below.

Peptides of the present invention may also comprise epitopes that bind to MHC class II DR molecules. A greater degree of heterogeneity in both size and binding frame position of the motif, relative to the N and C termini of the peptide, exists for class II peptide ligands. This increased heterogeneity of HLA class II peptide ligands is due to the structure of the binding groove of the HLA class II molecule which, unlike its class I counterpart, is open at both ends. Crystallographic analysis of HLA class II DRB*0101-peptide complexes showed that the major energy of binding is contributed by peptide residues complexed with complementary pockets on the DRB*0101 molecules. An important anchor residue engages the deepest hydrophobic pocket (*see, e.g.*, Madden, D.R. *Ann. Rev. Immunol.* 13:587, 1995) and is referred to as position 1 (P1). P1 may

represent the N-terminal residue of a class II binding peptide epitope, but more typically is flanked towards the N-terminus by one or more residues. Other studies have also pointed to an important role for the peptide residue in the 6th position towards the C-terminus, relative to P1, for binding to various DR molecules.

In the past few years evidence has accumulated to demonstrate that a large fraction of HLA class I and class II molecules can be classified into a relatively few supertypes, each characterized by largely overlapping peptide binding repertoires, and consensus structures of the main peptide binding pockets. Thus, peptides of the present invention are identified by any one of several HLA-specific amino acid motifs (*see, e.g.*, Tables I-III), or if the presence of the motif corresponds to the ability to bind several allele-specific HLA molecules, a supermotif. The HLA molecules that bind to peptides that possess a particular amino acid supermotif are collectively referred to as an HLA "supertype."

The peptide motifs and supermotifs described below, and summarized in Tables I-III, provide guidance for the identification and use of peptide epitopes in accordance with the invention.

Examples of peptide epitopes bearing a respective supermotif or motif are included in Tables as designated in the description of each motif or supermotif below. The Tables include a binding affinity ratio listing for some of the peptide epitopes. The ratio may be converted to IC_{50} by using the following formula: IC_{50} of the standard peptide/ratio = IC_{50} of the test peptide (*i.e.*, the peptide epitope). The IC_{50} values of standard peptides used to determine binding affinities for Class I peptides are shown in Table IV. The IC_{50} values of standard peptides used to determine binding affinities for Class II peptides are shown in Table V. The peptides used as standards for the binding assays described herein are examples of standards; alternative standard peptides can also be used when performing binding studies.

To obtain the peptide epitope sequences listed in each Table, protein sequence data for HER2/neu were evaluated for the presence of the designated supermotif or motif. The "pos" (position) column in the Tables designates the amino acid position in the HER2/neu protein that corresponds to the first amino acid residue of the putative epitope. The "number of amino acids" indicates the number of residues in the epitope sequence.

HLA Class I Motifs Indicative of CTL Inducing Peptide Epitopes:

The primary anchor residues of the HLA class I peptide epitope supermotifs and motifs delineated below are summarized in Table I. The HLA class I motifs set out in Table I(a) are those most particularly relevant to the invention claimed here. Primary and secondary anchor positions are summarized in Table II. Allele-specific HLA molecules that comprise HLA class I supertype families are listed in Table VI. In some cases, peptide epitopes may be listed in both a motif and a supermotif Table. The relationship of a particular motif and respective supermotif is indicated in the description of the individual motifs.

IV.D.1. HLA-A1 supermotif

The HLA-A1 supermotif is characterized by the presence in peptide ligands of a small (T or S) or hydrophobic (L, I, V, or M) primary anchor residue in position 2, and an aromatic (Y, F, or W) primary anchor residue at the C-terminal position of the epitope. The corresponding family of HLA molecules that bind to the A1 supermotif (*i.e.*, the HLA-A1 supertype) is comprised of at least: A*0101, A*2601, A*2602, A*2501, and A*3201 (*see, e.g.*, DiBrino, M. *et al.*, *J. Immunol.* 151:5930, 1993; DiBrino, M. *et al.*, *J. Immunol.* 152:620, 1994; Kondo, A. *et al.*, *Immunogenetics* 45:249, 1997). Other allele-specific HLA molecules predicted to be members of the A1 superfamily are shown in Table VI. Peptides binding to each of the individual HLA proteins can be modulated by substitutions at primary and/or secondary anchor positions, preferably choosing respective residues specified for the supermotif.

Representative peptide epitopes that comprise the A1 supermotif are set forth on the attached Table VII.

IV.D.2. HLA-A2 supermotif

Primary anchor specificities for allele-specific HLA-A2.1 molecules (*see, e.g.*, Falk *et al.*, *Nature* 351:290-296, 1991; Hunt *et al.*, *Science* 255:1261-1263, 1992; Parker *et al.*, *J. Immunol.* 149:3580-3587, 1992; Ruppert *et al.*, *Cell* 74:929-937, 1993) and cross-reactive binding among HLA-A2 and -A28 molecules have been described. (*See, e.g.*, Fruci *et al.*, *Human Immunol.* 38:187-192, 1993; Tanigaki *et al.*, *Human Immunol.* 39:155-162, 1994; Del Guercio *et al.*, *J. Immunol.* 154:685-693, 1995; Kast *et al.*, *J. Immunol.* 152:3904-3912, 1994 for reviews of relevant data.) These primary anchor residues define the HLA-A2 supermotif; which presence in peptide ligands corresponds

to the ability to bind several different HLA-A2 and -A28 molecules. The HLA-A2 supermotif comprises peptide ligands with L, I, V, M, A, T, or Q as a primary anchor residue at position 2 and L, I, V, M, A, or T as a primary anchor residue at the C-terminal position of the epitope.

The corresponding family of HLA molecules (*i.e.*, the HLA-A2 supertype that binds these peptides) is comprised of at least: A*0201, A*0202, A*0203, A*0204, A*0205, A*0206, A*0207, A*0209, A*0214, A*6802, and A*6901. Other allele-specific HLA molecules predicted to be members of the A2 superfamily are shown in Table VI. As explained in detail below, binding to each of the individual allele-specific HLA molecules can be modulated by substitutions at the primary anchor and/or secondary anchor positions, preferably choosing respective residues specified for the supermotif.

Representative peptide epitopes that comprise an A2 supermotif are set forth on the attached Table VIII. The motifs comprising the primary anchor residues V, A, T, or Q at position 2 and L, I, V, A, or T at the C-terminal position are those most particularly relevant to the invention claimed herein.

IV.D.3. HLA-A3 supermotif

The HLA-A3 supermotif is characterized by the presence in peptide ligands of A, L, I, V, M, S, or, T as a primary anchor at position 2, and a positively charged residue, R or K, at the C-terminal position of the epitope, *e.g.*, in position 9 of 9-mers (*see, e.g.*, Sidney *et al.*, *Hum. Immunol.* 45:79, 1996). Exemplary members of the corresponding family of HLA molecules (the HLA-A3 supertype) that bind the A3 supermotif include at least: A*0301, A*1101, A*3101, A*3301, and A*6801. Other allele-specific HLA molecules predicted to be members of the A3 supertype are shown in Table VI. As explained in detail below, peptide binding to each of the individual allele-specific HLA proteins can be modulated by substitutions of amino acids at the primary and/or secondary anchor positions of the peptide, preferably choosing respective residues specified for the supermotif.

Representative peptide epitopes that comprise the A3 supermotif are set forth on the attached Table IX.

IV.D.4. HLA-A24 supermotif

The HLA-A24 supermotif is characterized by the presence in peptide ligands of an aromatic (F, W, or Y) or hydrophobic aliphatic (L, I, V, M, or T) residue as a primary anchor in position 2, and Y, F, W, L, I, or M as primary anchor at the C-terminal position of the epitope (*see, e.g.*, Sette and Sidney, *Immunogenetics*, in press, 1999). The corresponding family of HLA molecules that bind to the A24 supermotif (*i.e.*, the A24 supertype) includes at least: A*2402, A*3001, and A*2301. Other allele-specific HLA molecules predicted to be members of the A24 supertype are shown in Table VI. Peptide binding to each of the allele-specific HLA molecules can be modulated by substitutions at primary and/or secondary anchor positions, preferably choosing respective residues specified for the supermotif.

Representative peptide epitopes that comprise the A24 supermotif are set forth on the attached Table X.

IV.D.5. HLA-B7 supermotif

The HLA-B7 supermotif is characterized by peptides bearing proline in position 2 as a primary anchor, and a hydrophobic or aliphatic amino acid (L, I, V, M, A, F, W, or Y) as the primary anchor at the C-terminal position of the epitope. The corresponding family of HLA molecules that bind the B7 supermotif (*i.e.*, the HLA-B7 supertype) is comprised of at least twenty six HLA-B proteins comprising at least: B*0702, B*0703, B*0704, B*0705, B*1508, B*3501, B*3502, B*3503, B*3504, B*3505, B*3506, B*3507, B*3508, B*5101, B*5102, B*5103, B*5104, B*5105, B*5301, B*5401, B*5501, B*5502, B*5601, B*5602, B*6701, and B*7801 (*see, e.g.,* Sidney, *et al., J. Immunol.* 154:247, 1995; Barber, *et al., Curr. Biol.* 5:179, 1995; Hill, *et al., Nature* 360:434, 1992; Rammensee, *et al., Immunogenetics* 41:178, 1995 for reviews of relevant data). Other allele-specific HLA molecules predicted to be members of the B7 supertype are shown in Table VI. As explained in detail below, peptide binding to each of the individual allele-specific HLA proteins can be modulated by substitutions at the primary and/or secondary anchor positions of the peptide, preferably choosing respective residues specified for the supermotif.

Representative peptide epitopes that comprise the B7 supermotif are set forth on the attached Table XI.

IV.D.6. HLA-B27 supermotif

The HLA-B27 supermotif is characterized by the presence in peptide ligands of a positively charged (R, H, or K) residue as a primary anchor at position 2, and a hydrophobic (F, Y, L, W, M, I, A, or V) residue as a primary anchor at the C-terminal position of the epitope (*see, e.g.*, Sidney and Sette, *Immunogenetics*, in press, 1999). Exemplary members of the corresponding family of HLA molecules that bind to the B27 supermotif (*i.e.*, the B27 supertype) include at least B*1401, B*1402, B*1509, B*2702, B*2703, B*2704, B*2705, B*2706, B*3801, B*3901, B*3902, and B*7301. Other allele-specific HLA molecules predicted to be members of the B27 supertype are shown in Table VI. Peptide binding to each of the allele-specific HLA molecules can be modulated by substitutions at primary and/or secondary anchor positions, preferably choosing respective residues specified for the supermotif.

Representative peptide epitopes that comprise the B27 supermotif are set forth on the attached Table XII.

IV.D.7. HLA-B44 supermotif

The HLA-B44 supermotif is characterized by the presence in peptide ligands of negatively charged (D or E) residues as a primary anchor in position 2, and hydrophobic residues (F, W, Y, L, I, M, V, or A) as a primary anchor at the C-terminal position of the epitope (*see, e.g.*, Sidney et al., *Immunol. Today* 17:261, 1996). Exemplary members of the corresponding family of HLA molecules that bind to the B44 supermotif (*i.e.*, the B44 supertype) include at least: B*1801, B*1802, B*3701, B*4001, B*4002, B*4006, B*4402, B*4403, and B*4404. Peptide binding to each of the allele-specific HLA molecules can be modulated by substitutions at primary and/or secondary anchor positions; preferably choosing respective residues specified for the supermotif.

IV.D.8. HLA-B58 supermotif

The HLA-B58 supermotif is characterized by the presence in peptide ligands of a small aliphatic residue (A, S, or T) as a primary anchor residue at position 2, and an aromatic or hydrophobic residue (F, W, Y, L, I, V, M, or A) as a primary anchor residue at the C-terminal position of the epitope (*see, e.g.*, Sidney and Sette, *Immunogenetics*, in press, 1999 for reviews of relevant data). Exemplary members of the corresponding family of HLA molecules that bind to the B58 supermotif (*i.e.*, the B58 supertype) include at least: B*1516, B*1517, B*5701, B*5702, and B*5801. Other allele-specific

HLA molecules predicted to be members of the B58 supertype are shown in Table VI. Peptide binding to each of the allele-specific HLA molecules can be modulated by substitutions at primary and/or secondary anchor positions, preferably choosing respective residues specified for the supermotif.

Representative peptide epitopes that comprise the B58 supermotif are set forth on the attached Table XIII.

IV.D.9. HLA-B62 supermotif

The HLA-B62 supermotif is characterized by the presence in peptide ligands of the polar aliphatic residue Q or a hydrophobic aliphatic residue (L, V, M, I, or P) as a primary anchor in position 2, and a hydrophobic residue (F, W, Y, M, I, V, L, or A) as a primary anchor at the C-terminal position of the epitope (*see, e.g.*, Sidney and Sette, *Immunogenetics*, in press, 1999). Exemplary members of the corresponding family of HLA molecules that bind to the B62 supermotif (*i.e.*, the B62 supertype) include at least: B*1501, B*1502, B*1513, and B5201. Other allele-specific HLA molecules predicted to be members of the B62 supertype are shown in Table VI. Peptide binding to each of the allele-specific HLA molecules can be modulated by substitutions at primary and/or secondary anchor positions, preferably choosing respective residues specified for the supermotif.

Representative peptide epitopes that comprise the B62 supermotif are set forth on the attached Table XIV.

IV.D.10. HLA-A1 motif

The HLA-A1 motif is characterized by the presence in peptide ligands of T, S, or M as a primary anchor residue at position 2 and the presence of Y as a primary anchor residue at the C-terminal position of the epitope. An alternative allele-specific A1 motif is characterized by a primary anchor residue at position 3 rather than position 2. This motif is characterized by the presence of D, E, A, or S as a primary anchor residue in position 3, and a Y as a primary anchor residue at the C-terminal position of the epitope (*see, e.g.*, DiBrino *et al.*, J. Immunol., 152:620, 1994; Kondo *et al.*, *Immunogenetics* 45:249, 1997; and Kubo *et al.*, *J. Immunol.* 152:3913, 1994 for reviews of relevant data). Peptide binding to HLA-A1 can be modulated by substitutions at primary and/or secondary anchor positions, preferably choosing respective residues specified for the motif.

Representative peptide epitopes that comprise either A1 motif are set forth on the attached Table XV. Those epitopes comprising T, S, or M at position 2 and Y at the C-terminal position are also included in the listing of HLA-A1 supermotif-bearing peptide epitopes listed in Table VII, as these residues are a subset of the A1 supermotif primary anchors.

IV.D.11. HLA-A*0201 motif

An HLA-A2*0201 motif was determined to be characterized by the presence in peptide ligands of L or M as a primary anchor residue in position 2, and L or V as a primary anchor residue at the C-terminal position of a 9-residue peptide (*see, e.g.*, Falk *et al.*, *Nature* 351:290-296, 1991) and was further found to comprise an I at position 2 and I or A at the C-terminal position of a nine amino acid peptide (*see, e.g.*, Hunt *et al.*, Science 255:1261-1263, March 6, 1992; Parker *et al.*, *J. Immunol.* 149:3580-3587, 1992). The A*0201 allele-specific motif has also been defined by the present inventors to additionally comprise V, A, T, or Q as a primary anchor residue at position 2, and M or T as a primary anchor residue at the C-terminal position of the epitope (*see, e.g.*, Kast *et al.*, *J. Immunol.* 152:3904-3912, 1994). Thus, the HLA-A*0201 motif comprises peptide ligands with L, I, V, M, A, T, or Q as primary anchor residues at position 2 and L, I, V, M, A, or T as a primary anchor residue at the C-terminal position of the epitope. The preferred and tolerated residues that characterize the primary anchor positions of the HLA-A*0201 motif are identical to the residues describing the A2 supermotif. (For reviews of relevant data, *see, e.g.*, del Guercio *et al.*, *J. Immunol.* 154:685-693, 1995; Ruppert *et al.*, *Cell* 74:929-937, 1993; Sidney *et al.*, *Immunol. Today* 17:261-266, 1996; Sette and Sidney, *Curr. Opin. in Immunol.* 10:478-482, 1998). Secondary anchor residues that characterize the A*0201 motif have additionally been defined (*see, e.g.*, Ruppert *et al.*, *Cell* 74:929-937, 1993). These are shown in Table II. Peptide binding to HLA-A*0201 molecules can be modulated by substitutions at primary and/or secondary anchor positions, preferably choosing respective residues specified for the motif.

Representative peptide epitopes that comprise an A*0201 motif are set forth on the attached Table VIII. The A*0201 motifs comprising the primary anchor residues V, A, T, or Q at position 2 and L, I, V, A, or T at the C-terminal position are those most particularly relevant to the invention claimed herein.

IV.D.12. HLA-A3 motif

The HLA-A3 motif is characterized by the presence in peptide ligands of L, M, V, I, S, A, T, F, C, G, or D as a primary anchor residue at position 2, and the presence of K, sY, R, H, F, or A as a primary anchor residue at the C-terminal position of the epitope (*see, e.g.*, DiBrino *et al.*, *Proc. Natl. Acad. Sci USA* 90:1508, 1993; and Kubo *et al.*, *J. Immunol.* 152:3913-3924, 1994). Peptide binding to HLA-A3 can be modulated by substitutions at primary and/or secondary anchor positions, preferably choosing respective residues specified for the motif.

Representative peptide epitopes that comprise the A3 motif are set forth on the attached Table XVI. Those peptide epitopes that also comprise the A3 supermotif are also listed in Table IX. The A3 supermotif primary anchor residues comprise a subset of the A3- and A11-allele specific motif primary anchor residues.

IV.D.13. HLA-A11 motif

The HLA-A11 motif is characterized by the presence in peptide ligands of V, T, M, L, I, S, A, G, N, C, D, or F as a primary anchor residue in position 2, and K, R, Y, or H as a primary anchor residue at the C-terminal position of the epitope (*see, e.g.*, Zhang *et al.*, *Proc. Natl. Acad. Sci USA* 90:2217-2221, 1993; and Kubo *et al.*, *J. Immunol.* 152:3913-3924, 1994). Peptide binding to HLA-A11 can be modulated by substitutions at primary and/or secondary anchor positions, preferably choosing respective residues specified for the motif.

Representative peptide epitopes that comprise the A11 motif are set forth on the attached Table XVII; peptide epitopes comprising the A3 allele-specific motif are also present in this Table because of the extensive overlap between the A3 and A11 motif primary anchor specificities. Further, those peptide epitopes that comprise the A3 supermotif are also listed in Table IX.

IV.D.14. HLA-A24 motif

The HLA-A24 motif is characterized by the presence in peptide ligands of Y, F, W, or M as a primary anchor residue in position 2, and F, L, I, or W as a primary anchor residue at the C-terminal position of the epitope (*see, e.g.*, *Kondo et al.*, *J. Immunol.* 155:4307-4312, 1995; and Kubo *et al.*, *J. Immunol.* 152:3913-3924, 1994). Peptide binding to HLA-A24 molecules can be modulated by substitutions at primary and/or

secondary anchor positions; preferably choosing respective residues specified for the motif.

Representative peptide epitopes that comprise the A24 motif are set forth on the attached Table XVIII. These epitopes are also listed in Table X, which sets forth HLA-A24-supermotif-bearing peptide epitopes, as the primary anchor residues characterizing the A24 allele-specific motif comprise a subset of the A24 supermotif primary anchor residues.

Motifs Indicative of Class II HTL Inducing Peptide Epitopes

The primary and secondary anchor residues of the HLA class II peptide epitope supermotifs and motifs delineated below are summarized in Table III.

IV.D.15. HLA DR-1-4-7 supermotif

Motifs have also been identified for peptides that bind to three common HLA class II allele-specific HLA molecules: HLA DRB1*0401, DRB1*0101, and DRB1*0701 (*see, e.g.*, the review by Southwood *et al. J. Immunology* 160:3363-3373,1998). Collectively, the common residues from these motifs delineate the HLA DR-1-4-7 supermotif. Peptides that bind to these DR molecules carry a supermotif characterized by a large aromatic or hydrophobic residue (Y, F, W, L, I, V, or M) as a primary anchor residue in position 1, and a small, non-charged residue (S, T, C, A, P, V, I, L, or M) as a primary anchor residue in position 6 of a 9-mer core region. Allele-specific secondary effects and secondary anchors for each of these HLA types have also been identified (Southwood *et al., supra*). These are set forth in Table III. Peptide binding to HLA-DRB1*0401, DRB1*0101, and/or DRB1*0701 can be modulated by substitutions at primary and/or secondary anchor positions, preferably choosing respective residues specified for the supermotif.

Potential epitope 9-mer core regions comprising the DR-1-4-7 supermotif, wherein position 1 of the supermotif is at position 1 of the nine-residue core, are set forth in Table XIX. Respective exemplary peptide epitopes of 15 amino acid residues in length, each of which comprise a nine residue core, are also shown, along with cross-reactive binding data for the exemplary 15-residue peptides.

IV.D.16. HLA DR3 motifs

Two alternative motifs (*i.e.*, submotifs) characterize peptide epitopes that bind to HLA-DR3 molecules (*see, e.g.*, Geluk *et al.*, *J. Immunol.* 152:5742, 1994). In the first motif (submotif DR3a) a large, hydrophobic residue (L, I, V, M, F, or Y) is present in anchor position 1 of a 9-mer core, and D is present as an anchor at position 4, towards the carboxyl terminus of the epitope. As in other class II motifs, core position 1 may or may not occupy the peptide N-terminal position.

The alternative DR3 submotif provides for lack of the large, hydrophobic residue at anchor position 1, and/or lack of the negatively charged or amide-like anchor residue at position 4, by the presence of a positive charge at position 6 towards the carboxyl terminus of the epitope. Thus, for the alternative allele-specific DR3 motif (submotif DR3b): L, I, V, M, F, Y, A, or Y is present at anchor position 1; D, N, Q, E, S, or T is present at anchor position 4; and K, R, or H is present at anchor position 6. Peptide binding to HLA-DR3 can be modulated by substitutions at primary and/or secondary anchor positions, preferably choosing respective residues specified for the motif.

Potential peptide epitope 9-mer core regions corresponding to a nine residue sequence comprising the DR3a submotif (wherein position 1 of the motif is at position 1 of the nine residue core) are set forth in Table XXa. Respective exemplary peptide epitopes of 15 amino acid residues in length, each of which comprise the nine residue core, are also shown in Table XXa along with binding data for the exemplary peptides.

Potential peptide epitope 9-mer core regions comprising the DR3b submotif and respective exemplary 15-mer peptides comprising the DR3 submotif-b epitope are set forth in Table XXb along with binding data for the exemplary peptides.

Each of the HLA class I or class II peptide epitopes set out in the Tables herein are deemed singly to be an inventive aspect of this application. Further, it is also an inventive aspect of this application that each peptide epitope may be used in combination with any other peptide epitope.

IV.E. Enhancing Population Coverage of the Vaccine

Vaccines that have broad population coverage are preferred because they are more commercially viable and generally applicable to the most people. Broad population coverage can be obtained using the peptides of the invention (and nucleic acid compositions that encode such peptides) through selecting peptide epitopes that bind to HLA alleles which, when considered in total, are present in most of the population. Table

XXI lists the overall frequencies of the HLA class I supertypes in various ethnicities (Table XXIa) and the combined population coverage achieved by the A2-, A3-, and B7-supertypes (Table XXIb). The A2-, A3-, and B7 supertypes are each present on the average of over 40% in each of these five major ethnic groups. Coverage in excess of 80% is achieved with a combination of these supermotifs. These results suggest that effective and non-ethnically biased population coverage is achieved upon use of a limited number of cross-reactive peptides. Although the population coverage reached with these three main peptide specificities is high, coverage can be expanded to reach 95% population coverage and above, and more easily achieve truly multispecific responses upon use of additional supermotif or allele-specific motif bearing peptides.

The B44-, A1-, and A24-supertypes are each present, on average, in a range from 25% to 40% in these major ethnic populations (Table XXIa). While less prevalent overall, the B27-, B58-, and B62 supertypes are each present with a frequency >25% in at least one major ethnic group (Table XXIa). Table XXIb summarizes the estimated prevalence of combinations of HLA supertypes that have been identified in five major ethnic groups. The incremental coverage obtained by the inclusion of A1,- A24-, and B44-supertypes to the A2, A3, and B7 coverage and coverage obtained with all of the supertypes described herein, is shown.

The data presented herein, together with the previous definition of the A2-, A3-, and B7-supertypes, indicates that all antigens, with the possible exception of A29, B8, and B46, can be classified into a total of nine HLA supertypes. By including epitopes from the six most frequent supertypes, an average population coverage of 99% is obtained for five major ethnic groups.

IV.F. Immune Response-Stimulating Peptide Analogs

In general, CTL and HTL responses are not directed against all possible epitopes. Rather, they are restricted to a few "immunodominant" determinants (Zinkernagel, *et al., Adv. Immunol.* 27:5159, 1979; Bennink, *et al., J. Exp. Med.* 168:19351939, 1988; Rawle, *et al., J. Immunol.* 146:3977-3984, 1991). It has been recognized that immunodominance (Benacerraf, *et al., Science* 175:273-279, 1972) could be explained by either the ability of a given epitope to selectively bind a particular HLA protein (determinant selection theory) (Vitiello, *et al., J. Immunol.* 131:1635, 1983); Rosenthal, *et al., Nature* 267:156-158, 1977), or to be selectively recognized by the existing TCR (T cell receptor) specificities (repertoire theory) (Klein, J., IMMUNOLOGY, THE SCIENCE OF SELF/NONSELF

DISCRIMINATION, John Wiley & Sons, New York, pp. 270-310, 1982). It has been demonstrated that additional factors, mostly linked to processing events, can also play a key role in dictating, beyond strict immunogenicity, which of the many potential determinants will be presented as immunodominant (Sercarz, *et al.*, *Annu. Rev. Immunol.* 11:729-766, 1993).

Because tissue specific and developmental TAAs are expressed on normal tissue at least at some point in time or location within the body, it may be expected that T cells to them, particularly dominant epitopes, are eliminated during immunological surveillance and that tolerance is induced. However, CTL responses to tumor epitopes in both normal donors and cancer patient has been detected, which may indicate that tolerance is incomplete (*see, e.g.*, Kawashima *et al.*, Hum. Immunol. 59:1, 1998; Tsang, *J. Natl. Cancer Inst.* 87:82-90, 1995; Rongcun *et al.*, *J. Immunol.* 163:1037, 1999). Thus, immune tolerance does not completely eliminate or inactivate CTL precursors capable of recognizing high affinity HLA class I binding peptides.

An additional strategy to overcome tolerance is to use analog peptides. Without intending to be bound by theory, it is believed that because T cells to dominant epitopes may have been clonally deleted, selecting subdominant epitopes may allow existing T cells to be recruited, which will then lead to a therapeutic or prophylactic response. However, the binding of HLA molecules to subdominant epitopes is often less vigorous than to dominant ones. Accordingly, there is a need to be able to modulate the binding affinity of particular immunogenic epitopes for one or more HLA molecules, and thereby to modulate the immune response elicited by the peptide, for example to prepare analog peptides which elicit a more vigorous response.

Although peptides with suitable cross-reactivity among all alleles of a superfamily are identified by the screening procedures described above, cross-reactivity is not always as complete as possible, and in certain cases procedures to increase cross-reactivity of peptides can be useful; moreover, such procedures can also be used to modify other properties of the peptides such as binding affinity or peptide stability. Having established the general rules that govern cross-reactivity of peptides for HLA alleles within a given motif or supermotif, modification (*i.e.*, analoging) of the structure of peptides of particular interest in order to achieve broader (or otherwise modified) HLA binding capacity can be performed. More specifically, peptides which exhibit the broadest cross-reactivity patterns, can be produced in accordance with the teachings herein. The present

concepts related to analog generation are set forth in greater detail in co-pending U.S.S.N. 09/226,775 filed 1/6/99.

In brief, the strategy employed utilizes the motifs or supermotifs which correlate with binding to certain HLA molecules. The motifs or supermotifs are defined by having primary anchors, and in many cases secondary anchors. Analog peptides can be created by substituting amino acid residues at primary anchor, secondary anchor, or at primary and secondary anchor positions. Generally, analogs are made for peptides that already bear a motif or supermotif. Preferred secondary anchor residues of supermotifs and motifs that have been defined for HLA class I and class II binding peptides are shown in Tables II and III, respectively.

For a number of the motifs or supermotifs in accordance with the invention, residues are defined which are deleterious to binding to allele-specific HLA molecules or members of HLA supertypes that bind the respective motif or supermotif (Tables II and III). Accordingly, removal of such residues that are detrimental to binding can be performed in accordance with the present invention. For example, in the case of the A3 supertype, when all peptides that have such deleterious residues are removed from the population of peptides used in the analysis, the incidence of cross-reactivity increased from 22% to 37% (*see, e.g.*, Sidney, J. *et al.*, *Hu. Immunol.* 45:79, 1996). Thus, one strategy to improve the cross-reactivity of peptides within a given supermotif is simply to delete one or more of the deleterious residues present within a peptide and substitute a small "neutral" residue such as Ala (that may not influence T cell recognition of the peptide). An enhanced likelihood of cross-reactivity is expected if, together with elimination of detrimental residues within a peptide, "preferred" residues associated with high affinity binding to an allele-specific HLA molecule or to multiple HLA molecules within a superfamily are inserted.

To ensure that an analog peptide, when used as a vaccine, actually elicits a CTL response to the native epitope *in vivo* (or, in the case of class II epitopes, elicits helper T cells that cross-react with the wild type peptides), the analog peptide may be used to immunize T cells *in vitro* from individuals of the appropriate HLA allele. Thereafter, the immunized cells' capacity to induce lysis of wild type peptide sensitized target cells is evaluated. It will be desirable to use as antigen presenting cells, cells that have been either infected, or transfected with the appropriate genes, or, in the case of class II epitopes only, cells that have been pulsed with whole protein antigens, to establish whether endogenously produced antigen is also recognized by the relevant T cells.

Another embodiment of the invention is to create analogs of weak binding peptides, to thereby ensure adequate numbers of cross-reactive cellular binders. Class I binding peptides exhibiting binding affinities of 500-5000 nM, and carrying an acceptable but suboptimal primary anchor residue at one or both positions can be "fixed" by substituting preferred anchor residues in accordance with the respective supertype. The analog peptides can then be tested for crossbinding activity.

Another embodiment for generating effective peptide analogs involves the substitution of residues that have an adverse impact on peptide stability or solubility in, *e.g.*, a liquid environment. This substitution may occur at any position of the peptide epitope. For example, a cysteine can be substituted out in favor of α-amino butyric acid ("B" in the single letter abbreviations for peptide sequences listed herein). Due to its chemical nature, cysteine has the propensity to form disulfide bridges and sufficiently alter the peptide structurally so as to reduce binding capacity. Substituting α-amino butyric acid for cysteine not only alleviates this problem, but actually improves binding and crossbinding capability in certain instances (*see, e.g.*, the review by Sette *et al.*, In: Persistent Viral Infections, Eds. R. Ahmed and I. Chen, John Wiley & Sons, England, 1999).

Representative analog peptides are set forth in Table XXII. The Table indicates the length and sequence of the analog peptide as well as the motif or supermotif, if appropriate. The information in the "Fixed Nomenclature" column indicates the residues substituted at the indicated position numbers for the respective analog.

IV.G. Computer Screening of Protein Sequences from Disease-Related Antigens for Supermotif- or Motif-Bearing Peptides

In order to identify supermotif- or motif-bearing epitopes in a target antigen, a native protein sequence, *e.g.*, a tumor-associated antigen, or sequences from an infectious organism, or a donor tissue for transplantation, is screened using a means for computing, such as an intellectual calculation or a computer, to determine the presence of a supermotif or motif within the sequence. The information obtained from the analysis of native peptide can be used directly to evaluate the status of the native peptide or may be utilized subsequently to generate the peptide epitope.

Computer programs that allow the rapid screening of protein sequences for the occurrence of the subject supermotifs or motifs are encompassed by the present invention; as are programs that permit the generation of analog peptides. These programs

are implemented to analyze any identified amino acid sequence or operate on an unknown sequence and simultaneously determine the sequence and identify motif-bearing epitopes thereof; analogs can be simultaneously determined as well. Generally, the identified sequences will be from a pathogenic organism or a tumor-associated peptide. For example, the target TAA molecules include, without limitation, CEA, MAGE, p53 and HER2/neu.

It is important that the selection criteria utilized for prediction of peptide binding are as accurate as possible, to correlate most efficiently with actual binding. Prediction of peptides that bind, for example, to HLA-A*0201, on the basis of the presence of the appropriate primary anchors, is positive at about a 30% rate (*see, e.g.*, Ruppert, J. *et al. Cell* 74:929, 1993). However, by extensively analyzing peptide-HLA binding data disclosed herein, data in related patent applications, and data in the art, the present inventors have developed a number of allele-specific polynomial algorithms that dramatically increase the predictive value over identification on the basis of the presence of primary anchor residues alone. These algorithms take into account not only the presence or absence of primary anchors, but also consider the positive or deleterious presence of secondary anchor residues (to account for the impact of different amino acids at different positions). The algorithms are essentially based on the premise that the overall affinity (or ΔG) of peptide-HLA interactions can be approximated as a linear polynomial function of the type:

$$\Delta G = a_{1i} \times a_{2i} \times a_{3i} \ldots \times a_{ni}$$

where a_{ji} is a coefficient that represents the effect of the presence of a given amino acid (j) at a given position (i) along the sequence of a peptide of n amino acids. An important assumption of this method is that the effects at each position are essentially independent of each other. This assumption is justified by studies that demonstrated that peptides are bound to HLA molecules and recognized by T cells in essentially an extended conformation. Derivation of specific algorithm coefficients has been described, for example, in Gulukota, K. *et al., J. Mol. Biol.* 267:1258, 1997.

Additional methods to identify preferred peptide sequences, which also make use of specific motifs, include the use of neural networks and molecular modeling programs (*see, e.g.*, Milik *et al., Nature Biotechnology* 16:753, 1998; Altuvia *et al., Hum. Immunol.* 58:1, 1997; Altuvia *et al, J. Mol. Biol.* 249:244, 1995; Buus, S. *Curr. Opin. Immunol.* 11:209-213, 1999; Brusic, V. *et al., Bioinformatics* 14:121-130, 1998; Parker *et al., J.*

Immunol. 152:163, 1993; Meister *et al.*, *Vaccine* 13:581, 1995; Hammer *et al.*, *J. Exp. Med.* 180:2353, 1994; Sturniolo *et al.*, *Nature Biotechnol.* 17:555 1999).

For example, it has been shown that in sets of A*0201 motif-bearing peptides containing at least one preferred secondary anchor residue while avoiding the presence of any deleterious secondary anchor residues, 69% of the peptides will bind A*0201 with an IC_{50} less than 500 nM (Ruppert, J. *et al. Cell* 74:929, 1993). These algorithms are also flexible in that cut-off scores may be adjusted to select sets of peptides with greater or lower predicted binding properties, as desired.

In utilizing computer screening to identify peptide epitopes, a protein sequence or translated sequence may be analyzed using software developed to search for motifs, for example the "FINDPATTERNS' program (Devereux, *et al. Nucl. Acids Res.* 12:387-395, 1984) or MotifSearch 1.4 software program (D. Brown, San Diego, CA) to identify potential peptide sequences containing appropriate HLA binding motifs. The identified peptides can be scored using customized polynomial algorithms to predict their capacity to bind specific HLA class I or class II alleles. As appreciated by one of ordinary skill in the art, a large array of computer programming software and hardware options are available in the relevant art which can be employed to implement the motifs of the invention in order to evaluate (*e.g.*, without limitation, to identify epitopes, identify epitope concentration per peptide length, or to generate analogs) known or unknown peptide sequences.

In accordance with the procedures described above, HER2/neu peptide epitopes and analogs thereof that are able to bind HLA supertype groups or allele-specific HLA molecules have been identified (Tables VII-XX; Table XXII).

IV.H. Preparation of Peptide Epitopes

Peptides in accordance with the invention can be prepared synthetically, by recombinant DNA technology or chemical synthesis, or from natural sources such as native tumors or pathogenic organisms. Peptide epitopes may be synthesized individually or as polyepitopic peptides. Although the peptide will preferably be substantially free of other naturally occurring host cell proteins and fragments thereof, in some embodiments the peptides may be synthetically conjugated to native fragments or particles.

The peptides in accordance with the invention can be a variety of lengths, and either in their neutral (uncharged) forms or in forms which are salts. The peptides in accordance with the invention are either free of modifications such as glycosylation, side

chain oxidation, or phosphorylation; or they contain these modifications, subject to the condition that modifications do not destroy the biological activity of the peptides as described herein.

Desirably, the peptide epitope will be as small as possible while still maintaining substantially all of the immunologic activity of the native protein. When possible, it may be desirable to optimize HLA class I binding peptide epitopes of the invention to a length of about 8 to about 13 amino acid residues, preferably 9 to 10. HLA class II binding peptide epitopes may be optimized to a length of about 6 to about 30 amino acids in length, preferably to between about 13 and about 20 residues. Preferably, the peptide epitopes are commensurate in size with endogenously processed pathogen-derived peptides or tumor cell peptides that are bound to the relevant HLA molecules.

The identification and preparation of peptides of other lengths can also be carried out using the techniques described herein. Moreover, it is preferred to identify native peptide regions that contain a high concentration of class I and/or class II epitopes. Such a sequence is generally selected on the basis that it contains the greatest number of epitopes per amino acid length. It is to be appreciated that epitopes can be present in a frame-shifted manner, *e.g.* a 10 amino acid long peptide could contain two 9 amino acid long epitopes and one 10 amino acid long epitope; upon intracellular processing, each epitope can be exposed and bound by an HLA molecule upon administration of such a peptide. This larger, preferably multi-epitopic, peptide can be generated synthetically, recombinantly, or via cleavage from the native source.

The peptides of the invention can be prepared in a wide variety of ways. For the preferred relatively short size, the peptides can be synthesized in solution or on a solid support in accordance with conventional techniques. Various automatic synthesizers are commercially available and can be used in accordance with known protocols. (*See*, for example, Stewart & Young, SOLID PHASE PEPTIDE SYNTHESIS, 2D. ED., Pierce Chemical Co., 1984). Further, individual peptide epitopes can be joined using chemical ligation to produce larger peptides that are still within the bounds of the invention.

Alternatively, recombinant DNA technology can be employed wherein a nucleotide sequence which encodes an immunogenic peptide of interest is inserted into an expression vector, transformed or transfected into an appropriate host cell and cultivated under conditions suitable for expression. These procedures are generally known in the art, as described generally in Sambrook *et al.*, MOLECULAR CLONING, A LABORATORY MANUAL, Cold Spring Harbor Press, Cold Spring Harbor, New York (1989). Thus,

recombinant polypeptides which comprise one or more peptide sequences of the invention can be used to present the appropriate T cell epitope.

The nucleotide coding sequence for peptide epitopes of the preferred lengths contemplated herein can be synthesized by chemical techniques, for example, the phosphotriester method of Matteucci, *et al., J. Am. Chem. Soc.* 103:3185 (1981). Peptide analogs can be made simply by substituting the appropriate and desired nucleic acid base(s) for those that encode the native peptide sequence; exemplary nucleic acid substitutions are those that encode an amino acid defined by the motifs/supermotifs herein. The coding sequence can then be provided with appropriate linkers and ligated into expression vectors commonly available in the art, and the vectors used to transform suitable hosts to produce the desired fusion protein. A number of such vectors and suitable host systems are now available. For expression of the fusion proteins, the coding sequence will be provided with operably linked start and stop codons, promoter and terminator regions and usually a replication system to provide an expression vector for expression in the desired cellular host. For example, promoter sequences compatible with bacterial hosts are provided in plasmids containing convenient restriction sites for insertion of the desired coding sequence. The resulting expression vectors are transformed into suitable bacterial hosts. Of course, yeast, insect or mammalian cell hosts may also be used, employing suitable vectors and control sequences.

IV.I. Assays to Detect T-Cell Responses

Once HLA binding peptides are identified, they can be tested for the ability to elicit a T-cell response. The preparation and evaluation of motif-bearing peptides are described in PCT publications WO 94/20127 and WO 94/03205. Briefly, peptides comprising epitopes from a particular antigen are synthesized and tested for their ability to bind to the appropriate HLA proteins. These assays may involve evaluating the binding of a peptide of the invention to purified HLA class I molecules in relation to the binding of a radioiodinated reference peptide. Alternatively, cells expressing empty class I molecules (*i.e.* lacking peptide therein) may be evaluated for peptide binding by immunofluorescent staining and flow microfluorimetry. Other assays that may be used to evaluate peptide binding include peptide-dependent class I assembly assays and/or the inhibition of CTL recognition by peptide competition. Those peptides that bind to the class I molecule, typically with an affinity of 500 nM or less, are further evaluated for

their ability to serve as targets for CTLs derived from infected or immunized individuals, as well as for their capacity to induce primary *in vitro* or *in vivo* CTL responses that can give rise to CTL populations capable of reacting with selected target cells associated with a disease. Corresponding assays are used for evaluation of HLA class II binding peptides. HLA class II motif-bearing peptides that are shown to bind, typically at an affinity of 1000 nM or less, are further evaluated for the ability to stimulate HTL responses.

Conventional assays utilized to detect T cell responses include proliferation assays, lymphokine secretion assays, direct cytotoxicity assays, and limiting dilution assays. For example, antigen-presenting cells that have been incubated with a peptide can be assayed for the ability to induce CTL responses in responder cell populations. Antigen-presenting cells can be normal cells such as peripheral blood mononuclear cells or dendritic cells. Alternatively, mutant non-human mammalian cell lines that are deficient in their ability to load class I molecules with internally processed peptides and that have been transfected with the appropriate human class I gene, may be used to test for the capacity of the peptide to induce *in vitro* primary CTL responses.

Peripheral blood mononuclear cells (PBMCs) may be used as the responder cell source of CTL precursors. The appropriate antigen-presenting cells are incubated with peptide, after which the peptide-loaded antigen-presenting cells are then incubated with the responder cell population under optimized culture conditions. Positive CTL activation can be determined by assaying the culture for the presence of CTLs that kill radio-labeled target cells, both specific peptide-pulsed targets as well as target cells expressing endogenously processed forms of the antigen from which the peptide sequence was derived.

More recently, a method has been devised which allows direct quantification of antigen-specific T cells by staining with Fluorescein-labelled HLA tetrameric complexes (Altman, J. D. *et al.*, *Proc. Natl. Acad. Sci. USA* 90:10330, 1993; Altman, J. D. *et al.*, *Science* 274:94, 1996). Other relatively recent technical developments include staining for intracellular lymphokines, and interferon-γ release assays or ELISPOT assays. Tetramer staining, intracellular lymphokine staining and ELISPOT assays all appear to be at least 10-fold more sensitive than more conventional assays (Lalvani, A. *et al.*, *J. Exp. Med.* 186:859, 1997; Dunbar, P. R. *et al.*, *Curr. Biol.* 8:413, 1998; Murali-Krishna, K. *et al.*, *Immunity* 8:177, 1998).

HTL activation may also be assessed using such techniques known to those in the art such as T cell proliferation and secretion of lymphokines, *e.g.* IL-2 (*see*, *e.g.* Alexander *et al.*, Immunity 1:751-761, 1994).

Alternatively, immunization of HLA transgenic mice can be used to determine immunogenicity of peptide epitopes. Several transgenic mouse models including mice with human A2.1, A11 (which can additionally be used to analyze HLA-A3 epitopes), and B7 alleles have been characterized and others (*e.g.*, transgenic mice for HLA-A1 and A24) are being developed. HLA-DR1 and HLA-DR3 mouse models have also been developed. Additional transgenic mouse models with other HLA alleles may be generated as necessary. Mice may be immunized with peptides emulsified in Incomplete Freund's Adjuvant and the resulting T cells tested for their capacity to recognize peptide-pulsed target cells and target cells transfected with appropriate genes. CTL responses may be analyzed using cytotoxicity assays described above. Similarly, HTL responses may be analyzed using such assays as T cell proliferation or secretion of lymphokines.

Exemplary immunogenic peptide epitopes are set out in Table XXIII.

IV.J. Use of Peptide Epitopes as Diagnostic Agents and for Evaluating Immune Responses

HLA class I and class II binding peptides as described herein can be used, in one embodiment of the invention, as reagents to evaluate an immune response. The immune response to be evaluated may be induced by using as an immunogen any agent that may result in the production of antigen-specific CTLs or HTLs that recognize and bind to the peptide epitope(s) to be employed as the reagent. The peptide reagent need not be used as the immunogen. Assay systems that may be used for such an analysis include relatively recent technical developments such as tetramers, staining for intracellular lymphokines and interferon release assays, or ELISPOT assays.

For example, a peptide of the invention may be used in a tetramer staining assay to assess peripheral blood mononuclear cells for the presence of antigen-specific CTLs following exposure to a tumor cell antigen or an immunogen. The HLA-tetrameric complex is used to directly visualize antigen-specific CTLs (*see*, *e.g.*, Ogg *et al.*, *Science* 279:2103-2106, 1998; and Altman *et al.*, *Science* 174:94-96, 1996) and determine the frequency of the antigen-specific CTL population in a sample of peripheral blood mononuclear cells. A tetramer reagent using a peptide of the invention may be generated as follows: A peptide that binds to an HLA molecule is refolded in the presence of the

corresponding HLA heavy chain and β_2-microglobulin to generate a trimolecular complex. The complex is biotinylated at the carboxyl terminal end of the heavy chain at a site that was previously engineered into the protein. Tetramer formation is then induced by the addition of streptavidin. By means of fluorescently labeled streptavidin, the tetramer can be used to stain antigen-specific cells. The cells may then be identified, for example, by flow cytometry. Such an analysis may be used for diagnostic or prognostic purposes.

Peptides of the invention may also be used as reagents to evaluate immune recall responses (*see, e.g.*, Bertoni *et al.*, *J. Clin. Invest.* 100:503-513, 1997 and Penna *et al.*, *J. Exp. Med.* 174:1565-1570, 1991). For example, patient PBMC samples from individuals with cancer may be analyzed for the presence of antigen-specific CTLs or HTLs using specific peptides. A blood sample containing mononuclear cells may be evaluated by cultivating the PBMCs and stimulating the cells with a peptide of the invention. After an appropriate cultivation period, the expanded cell population may be analyzed, for example, for CTL or for HTL activity.

The peptides may also be used as reagents to evaluate the efficacy of a vaccine. PBMCs obtained from a patient vaccinated with an immunogen may be analyzed using, for example, either of the methods described above. The patient is HLA typed, and peptide epitope reagents that recognize the allele-specific molecules present in that patient are selected for the analysis. The immunogenicity of the vaccine is indicated by the presence of epitope-specific CTLs and/or HTLs in the PBMC sample.

The peptides of the invention may also be used to make antibodies, using techniques well known in the art (see, *e.g.* *CURRENT PROTOCOLS IN IMMUNOLOGY*, Wiley/Greene, NY; and *Antibodies A Laboratory Manual,* Harlow and Lane, Cold Spring Harbor Laboratory Press, 1989), which may be useful as reagents to diagnose or monitor cancer. Such antibodies include those that recognize a peptide in the context of an HLA molecule, *i.e.*, antibodies that bind to a peptide-MHC complex.

IV.K. Vaccine Compositions

Vaccines that contain an immunogenically effective amount of one or more peptides as described herein are a further embodiment of the invention. Once appropriately immunogenic epitopes have been defined, they can be sorted and delivered by various means, herein referred to as "vaccine" compositions. Such vaccine

compositions can include, for example, lipopeptides (*e.g.*,Vitiello, A. *et al.*, *J. Clin. Invest.* 95:341, 1995), peptide compositions encapsulated in poly(DL-lactide-co-glycolide) ("PLG") microspheres (*see, e.g.*, Eldridge, *et al.*, *Molec. Immunol.* 28:287-294, 1991: Alonso *et al.*, *Vaccine* 12:299-306, 1994; Jones *et al.*, *Vaccine* 13:675-681, 1995), peptide compositions contained in immune stimulating complexes (ISCOMS) (*see, e.g.*, Takahashi *et al.*, *Nature* 344:873-875, 1990; Hu *et al.*, *Clin Exp Immunol.* 113:235-243, 1998), multiple antigen peptide systems (MAPs) (*see e.g.*, Tam, J. P., *Proc. Natl. Acad. Sci. U.S.A.* 85:5409-5413, 1988; Tam, J.P., *J. Immunol. Methods* 196:17-32, 1996), viral delivery vectors (Perkus, M. E. *et al.*, In: *Concepts in vaccine development*, Kaufmann, S. H. E., ed., p. 379, 1996; Chakrabarti, S. *et al.*, *Nature* 320:535, 1986; Hu, S. L. *et al.*, *Nature* 320:537, 1986; Kieny, M.-P. *et al.*, *AIDS Bio/Technology* 4:790, 1986; Top, F. H. *et al.*, *J. Infect. Dis.* 124:148, 1971; Chanda, P. K. *et al.*, *Virology* 175:535, 1990), particles of viral or synthetic origin (*e.g.*, Kofler, N. *et al.*, *J. Immunol. Methods.* 192:25, 1996; Eldridge, J. H. *et al.*, *Sem. Hematol.* 30:16, 1993; Falo, L. D., Jr. *et al.*, *Nature Med.* 7:649, 1995), adjuvants (Warren, H. S., Vogel, F. R., and Chedid, L. A. *Annu. Rev. Immunol.* 4:369, 1986; Gupta, R. K. *et al.*, *Vaccine* 11:293, 1993), liposomes (Reddy, R. *et al.*, *J. Immunol.* 148:1585, 1992; Rock, K. L., *Immunol. Today* 17:131, 1996), or, naked or particle absorbed cDNA (Ulmer, J. B. *et al.*, *Science* 259:1745, 1993; Robinson, H. L., Hunt, L. A., and Webster, R. G., *Vaccine* 11:957, 1993; Shiver, J. W. *et al.*, In: *Concepts in vaccine development*, Kaufmann, S. H. E., ed., p. 423, 1996; Cease, K. B., and Berzofsky, J. A., *Annu. Rev. Immunol.* 12:923, 1994 and Eldridge, J. H. *et al.*, *Sem. Hematol.* 30:16, 1993). Toxin-targeted delivery technologies, also known as receptor mediated targeting, such as those of Avant Immunotherapeutics, Inc. (Needham, Massachusetts) may also be used.

Furthermore, vaccines in accordance with the invention encompass compositions of one or more of the claimed peptide(s). The peptide(s) can be individually linked to its own carrier; alternatively, the peptide(s) can exist as a homopolymer or heteropolymer of active peptide units. Such a polymer has the advantage of increased immunological reaction and, where different peptide epitopes are used to make up the polymer, the additional ability to induce antibodies and/or CTLs that react with different antigenic determinants of the pathogenic organism or tumor-related peptide targeted for an immune response. The composition may be a naturally occurring region of an antigen or may be prepared, *e.g.*, recombinantly or by chemical synthesis.

Furthermore, useful carriers that can be used with vaccines of the invention are well known in the art, and include, *e.g.*, thyroglobulin, albumins such as human serum albumin, tetanus toxoid, polyamino acids such as poly L-lysine, poly L-glutamic acid, influenza, hepatitis B virus core protein, and the like. The vaccines can contain a physiologically tolerable (*i.e.*, acceptable) diluent such as water, or saline, preferably phosphate buffered saline. The vaccines also typically include an adjuvant. Adjuvants such as incomplete Freund's adjuvant, aluminum phosphate, aluminum hydroxide, or alum are examples of materials well known in the art. Additionally, as disclosed herein, CTL responses can be primed by conjugating peptides of the invention to lipids, such as tripalmitoyl-S-glycerylcysteinlyseryl- serine (P_3CSS).

As disclosed in greater detail herein, upon immunization with a peptide composition in accordance with the invention, via injection, aerosol, oral, transdermal, transmucosal, intrapleural, intrathecal, or other suitable routes, the immune system of the host responds to the vaccine by producing large amounts of CTLs and/or HTLs specific for the desired antigen. Consequently, the host becomes at least partially immune to later infection, or at least partially resistant to developing an ongoing chronic infection, or derives at least some therapeutic benefit when the antigen was tumor-associated.

In some instances it may be desirable to combine the class I peptide vaccines of the invention with vaccines which induce or facilitate neutralizing antibody responses to the target antigen of interest, particularly to viral envelope antigens. A preferred embodiment of such a composition comprises class I and class II epitopes in accordance with the invention. An alternative embodiment of such a composition comprises a class I and/or class II epitope in accordance with the invention, along with a PADRE™ (Epimmune, San Diego, CA) molecule (described, for example, in U.S. Patent Number 5,736,142). Furthermore, any of these embodiments can be administered as a nucleic acid mediated modality.

For therapeutic or prophylactic immunization purposes, the peptides of the invention can also be expressed by viral or bacterial vectors. Examples of expression vectors include attenuated viral hosts, such as vaccinia or fowlpox. This approach involves the use of vaccinia virus, for example, as a vector to express nucleotide sequences that encode the peptides of the invention. Upon introduction into a host bearing a tumor, the recombinant vaccinia virus expresses the immunogenic peptide, and thereby elicits a host CTL and/or HTL response. Vaccinia vectors and methods useful in

immunization protocols are described in, *e.g.*, U.S. Patent No. 4,722,848. Another vector is BCG (Bacille Calmette Guerin). BCG vectors are described in Stover *et al.*, *Nature* 351:456-460 (1991). A wide variety of other vectors useful for therapeutic administration or immunization of the peptides of the invention, *e.g.* adeno and adeno-associated virus vectors, retroviral vectors, *Salmonella typhi* vectors, detoxified anthrax toxin vectors, and the like, will be apparent to those skilled in the art from the description herein.

Antigenic peptides are used to elicit a CTL and/or HTL response *ex vivo*, as well. The resulting CTL or HTL cells, can be used to treat chronic infections, or tumors in patients that do not respond to other conventional forms of therapy, or will not respond to a therapeutic vaccine peptide or nucleic acid in accordance with the invention. *Ex vivo* CTL or HTL responses to a particular antigen (infectious or tumor-associated antigen) are induced by incubating in tissue culture the patient's, or genetically compatible, CTL or HTL precursor cells together with a source of antigen-presenting cells (APC), such as dendritic cells, and the appropriate immunogenic peptide. After an appropriate incubation time (typically about 7-28 days), in which the precursor cells are activated and expanded into effector cells, the cells are infused back into the patient, where they will destroy (CTL) or facilitate destruction (HTL) of their specific target cell (an infected cell or a tumor cell). Transfected dendritic cells may also be used as antigen presenting cells. Alternatively, dendritic cells are transfected, *e.g.*, with a minigene construct in accordance with the invention, in order to elicit immune responses. Minigenes will be discussed in greater detail in a following section.

Vaccine compositions may also be administered *in vivo* in combination with dendritic cell mobilization whereby loading of dendritic cells occurs *in vivo*.

DNA or RNA encoding one or more of the peptides of the invention can also be administered to a patient. This approach is described, for instance, in Wolff *et. al.*, *Science* 247:1465 (1990) as well as U.S. Patent Nos. 5,580,859; 5,589,466; 5,804,566; 5,739,118; 5,736,524; 5,679,647; WO 98/04720; and in more detail below. Examples of DNA-based delivery technologies include "naked DNA", facilitated (bupivicaine, polymers, peptide-mediated) delivery, cationic lipid complexes, and particle-mediated ("gene gun") or pressure-mediated delivery (*see*, *e.g.*, U.S. Patent No. 5,922,687).

Preferably, the following principles are utilized when selecting an array of epitopes for inclusion in a polyepitopic composition for use in a vaccine, or for selecting discrete epitopes to be included in a vaccine and/or to be encoded by nucleic acids such as a minigene. Exemplary epitopes that may be utilized in a vaccine to treat or prevent

cancer are set out in Tables XXXVII and XXXVIII. It is preferred that each of the following principles are balanced in order to make the selection. The multiple epitopes to be incorporated in a given vaccine composition may be, but need not be, contiguous in sequence in the native antigen from which the epitopes are derived.

1.) Epitopes are selected which, upon administration, mimic immune responses that have been observed to be correlated with tumor clearance. For HLA Class I this includes 3-4 epitopes that come from at least one TAA. For HLA Class II a similar rationale is employed; again 3-4 epitopes are selected from at least one TAA (*see e.g.*, Rosenberg *et al.*, *Science* 278:1447-1450). Epitopes from one TAA may be used in combination with epitopes from one or more additional TAAs to produce a vaccine that targets tumors with varying expression patterns of frequently-expressed TAAs as described, *e.g.*, in Example 15.

2.) Epitopes are selected that have the requisite binding affinity established to be correlated with immunogenicity: for HLA Class I an IC_{50} of 500 nM or less, or for Class II an IC_{50} of 1000 nM or less.

3.) Sufficient supermotif bearing-peptides, or a sufficient array of allele-specific motif-bearing peptides, are selected to give broad population coverage. For example, it is preferable to have at least 80% population coverage. A Monte Carlo analysis, a statistical evaluation known in the art, can be employed to assess the breadth, or redundancy of, population coverage.

4.) When selecting epitopes from cancer-related antigens it is often preferred to select analogs because the patient may have developed tolerance to the native epitope. When selecting epitopes for infectious disease-related antigens it is preferable to select either native or analoged epitopes. Of particular relevance for infectious disease vaccines (but for cancer-related vaccines as well), are epitopes referred to as "nested epitopes." Nested epitopes occur where at least two epitopes overlap in a given peptide sequence. A peptide comprising "transcendent nested epitopes" is a peptide that has both HLA class I and HLA class II epitopes in it.

When providing nested epitopes, it is preferable to provide a sequence that has the greatest number of epitopes per provided sequence. Preferably, one avoids providing a peptide that is any longer than the amino terminus of the amino terminal epitope and the carboxyl terminus of the carboxyl terminal epitope in the peptide. When providing a longer peptide sequence, such as a sequence comprising nested epitopes, it is important to

screen the sequence in order to insure that it does not have pathological or other deleterious biological properties.

5.) When creating a minigene, as disclosed in greater detail in the following section, an objective is to generate the smallest peptide possible that encompasses the epitopes of interest. The principles employed are similar, if not the same as those employed when selecting a peptide comprising nested epitopes. Furthermore, upon determination of the nucleic acid sequence to be provided as a minigene, the peptide encoded thereby is analyzed to determine whether any "junctional epitopes" have been created. A junctional epitope is a potential HLA binding epitope, as predicted, *e.g.*, by motif analysis, that only exists because two discrete peptide sequences are encoded directly next to each other. Junctional epitopes are generally to be avoided because the recipient may bind to an HLA molecule and generate an immune response to that non-native epitope. Of particular concern is a junctional epitope that is a "dominant epitope." A dominant epitope may lead to such a zealous response that immune responses to other epitopes are diminished or suppressed.

IV.K.1. Minigene Vaccines

A growing body of experimental evidence demonstrates that a number of different approaches are available which allow simultaneous delivery of multiple epitopes. Nucleic acids encoding the peptides of the invention are a particularly useful embodiment of the invention. Epitopes for inclusion in a minigene are preferably selected according to the guidelines set forth in the previous section. A preferred means of administering nucleic acids encoding the peptides of the invention uses minigene constructs encoding a peptide comprising one or multiple epitopes of the invention. The use of multi-epitope minigenes is described below and in, *e.g.*, co-pending application U.S.S.N. 09/311,784; Ishioka *et al.*, *J. Immunol.* 162:3915-3925, 1999; An, L. and Whitton, J. L., *J. Virol.* 71:2292, 1997; Thomson, S. A. *et al.*, *J. Immunol.* 157:822, 1996; Whitton, J. L. *et al.*, *J. Virol.* 67:348, 1993; Hanke, R. *et al.*, *Vaccine* 16:426, 1998. For example, a multi-epitope DNA plasmid encoding supermotif- and/or motif-bearing HER2/neu epitopes derived from multiple regions of HER2/neu, the PADRE™ universal helper T cell epitope (or multiple HTL epitopes from HER2/neu), and an endoplasmic reticulum-translocating signal sequence can be engineered. A vaccine may also comprise epitopes, in addition to HER2/neu epitopes, that are derived from other TAAs.

The immunogenicity of a multi-epitopic minigene can be tested in transgenic mice to evaluate the magnitude of CTL induction responses against the epitopes tested. Further, the immunogenicity of DNA-encoded epitopes *in vivo* can be correlated with the *in vitro* responses of specific CTL lines against target cells transfected with the DNA plasmid. Thus, these experiments can show that the minigene serves to both: 1.) generate a CTL response and 2.) that the induced CTLs recognized cells expressing the encoded epitopes.

For example, to create a DNA sequence encoding the selected epitopes (minigene) for expression in human cells, the amino acid sequences of the epitopes may be reverse translated. A human codon usage table can be used to guide the codon choice for each amino acid. These epitope-encoding DNA sequences may be directly adjoined, so that when translated, a continuous polypeptide sequence is created. To optimize expression and/or immunogenicity, additional elements can be incorporated into the minigene design. Examples of amino acid sequences that can be reverse translated and included in the minigene sequence include: HLA class I epitopes, HLA class II epitopes, a ubiquitination signal sequence, and/or an endoplasmic reticulum targeting signal. In addition, HLA presentation of CTL and HTL epitopes may be improved by including synthetic (*e.g.* poly-alanine) or naturally-occurring flanking sequences adjacent to the CTL or HTL epitopes; these larger peptides comprising the epitope(s) are within the scope of the invention.

The minigene sequence may be converted to DNA by assembling oligonucleotides that encode the plus and minus strands of the minigene. Overlapping oligonucleotides (30-100 bases long) may be synthesized, phosphorylated, purified and annealed under appropriate conditions using well known techniques. The ends of the oligonucleotides can be joined, for example, using T4 DNA ligase. This synthetic minigene, encoding the epitope polypeptide, can then be cloned into a desired expression vector.

Standard regulatory sequences well known to those of skill in the art are preferably included in the vector to ensure expression in the target cells. Several vector elements are desirable: a promoter with a down-stream cloning site for minigene insertion; a polyadenylation signal for efficient transcription termination; an *E. coli* origin of replication; and an *E. coli* selectable marker (*e.g.* ampicillin or kanamycin resistance). Numerous promoters can be used for this purpose, *e.g.,* the human cytomegalovirus (hCMV) promoter. See, *e.g.*, U.S. Patent Nos. 5,580,859 and 5,589,466 for other suitable promoter sequences.

Additional vector modifications may be desired to optimize minigene expression and immunogenicity. In some cases, introns are required for efficient gene expression, and one or more synthetic or naturally-occurring introns could be incorporated into the transcribed region of the minigene. The inclusion of mRNA stabilization sequences and sequences for replication in mammalian cells may also be considered for increasing minigene expression.

Once an expression vector is selected, the minigene is cloned into the polylinker region downstream of the promoter. This plasmid is transformed into an appropriate *E. coli* strain, and DNA is prepared using standard techniques. The orientation and DNA sequence of the minigene, as well as all other elements included in the vector, are confirmed using restriction mapping and DNA sequence analysis. Bacterial cells harboring the correct plasmid can be stored as a master cell bank and a working cell bank.

In addition, immunostimulatory sequences (ISSs or CpGs) appear to play a role in the immunogenicity of DNA vaccines. These sequences may be included in the vector, outside the minigene coding sequence, if desired to enhance immunogenicity.

In some embodiments, a bi-cistronic expression vector which allows production of both the minigene-encoded epitopes and a second protein (included to enhance or decrease immunogenicity) can be used. Examples of proteins or polypeptides that could beneficially enhance the immune response if co-expressed include cytokines (*e.g.*, IL-2, IL-12, GM-CSF), cytokine-inducing molecules (*e.g.*, LeIF), costimulatory molecules, or for HTL responses, pan-DR binding proteins (PADRE™, Epimmune, San Diego, CA). Helper (HTL) epitopes can be joined to intracellular targeting signals and expressed separately from expressed CTL epitopes; this allows direction of the HTL epitopes to a cell compartment different than that of the CTL epitopes. If required, this could facilitate more efficient entry of HTL epitopes into the HLA class II pathway, thereby improving HTL induction. In contrast to HTL or CTL induction, specifically decreasing the immune response by co-expression of immunosuppressive molecules (*e.g.* TGF-β) may be beneficial in certain diseases.

Therapeutic quantities of plasmid DNA can be produced for example, by fermentation in *E. coli*, followed by purification. Aliquots from the working cell bank are used to inoculate growth medium, and grown to saturation in shaker flasks or a bioreactor according to well known techniques. Plasmid DNA can be purified using standard bioseparation technologies such as solid phase anion-exchange resins supplied by

QIAGEN, Inc. (Valencia, California). If required, supercoiled DNA can be isolated from the open circular and linear forms using gel electrophoresis or other methods.

Purified plasmid DNA can be prepared for injection using a variety of formulations. The simplest of these is reconstitution of lyophilized DNA in sterile phosphate-buffered saline (PBS). This approach, known as "naked DNA," is currently being used for intramuscular (IM) administration in clinical trials. To maximize the immunotherapeutic effects of minigene DNA vaccines, an alternative method for formulating purified plasmid DNA may be desirable. A variety of methods have been described, and new techniques may become available. Cationic lipids, glycolipids, and fusogenic liposomes can also be used in the formulation (see, *e.g.*, as described by WO 93/24640; Mannino & Gould-Fogerite, *BioTechniques* 6(7): 682 (1988); U.S. Pat No. 5,279,833; WO 91/06309; and Felgner, *et al., Proc. Nat'l Acad. Sci. USA* 84:7413 (1987). In addition, peptides and compounds referred to collectively as protective, interactive, non-condensing compounds (PINC) could also be complexed to purified plasmid DNA to influence variables such as stability, intramuscular dispersion, or trafficking to specific organs or cell types.

Target cell sensitization can be used as a functional assay for expression and HLA class I presentation of minigene-encoded CTL epitopes. For example, the plasmid DNA is introduced into a mammalian cell line that is suitable as a target for standard CTL chromium release assays. The transfection method used will be dependent on the final formulation. Electroporation can be used for "naked" DNA, whereas cationic lipids allow direct *in vitro* transfection. A plasmid expressing green fluorescent protein (GFP) can be co-transfected to allow enrichment of transfected cells using fluorescence activated cell sorting (FACS). These cells are then chromium-51 (^{51}Cr) labeled and used as target cells for epitope-specific CTL lines; cytolysis, detected by ^{51}Cr release, indicates both production of, and HLA presentation of, minigene-encoded CTL epitopes. Expression of HTL epitopes may be evaluated in an analogous manner using assays to assess HTL activity.

In vivo immunogenicity is a second approach for functional testing of minigene DNA formulations. Transgenic mice expressing appropriate human HLA proteins are immunized with the DNA product. The dose and route of administration are formulation dependent (*e.g.*, IM for DNA in PBS, intraperitoneal (IP) for lipid-complexed DNA). Twenty-one days after immunization, splenocytes are harvested and restimulated for one week in the presence of peptides encoding each epitope being tested. Thereafter, for CTL

effector cells, assays are conducted for cytolysis of peptide-loaded, ^{51}Cr-labeled target cells using standard techniques. Lysis of target cells that were sensitized by HLA loaded with peptide epitopes, corresponding to minigene-encoded epitopes, demonstrates DNA vaccine function for *in vivo* induction of CTLs. Immunogenicity of HTL epitopes is evaluated in transgenic mice in an analogous manner.

Alternatively, the nucleic acids can be administered using ballistic delivery as described, for instance, in U.S. Patent No. 5,204,253. Using this technique, particles comprised solely of DNA are administered. In a further alternative embodiment, DNA can be adhered to particles, such as gold particles.

IV.K.2. Combinations of CTL Peptides with Helper Peptides

Vaccine compositions comprising the peptides of the present invention, or analogs thereof, which have immunostimulatory activity may be modified to provide desired attributes, such as improved serum half-life, or to enhance immunogenicity.

For instance, the ability of a peptide to induce CTL activity can be enhanced by linking the peptide to a sequence which contains at least one epitope that is capable of inducing a T helper cell response. The use of T helper epitopes in conjunction with CTL epitopes to enhance immunogenicity is illustrated, for example, in the co-pending applications U.S.S.N. 08/820,360, U.S.S.N. 08/197,484, and U.S.S.N. 08/464,234.

Particularly preferred CTL epitope/HTL epitope conjugates are linked by a spacer molecule. The spacer is typically comprised of relatively small, neutral molecules, such as amino acids or amino acid mimetics, which are substantially uncharged under physiological conditions. The spacers are typically selected from, *e.g.*, Ala, Gly, or other neutral spacers of nonpolar amino acids or neutral polar amino acids. It will be understood that the optionally present spacer need not be comprised of the same residues and thus may be a hetero- or homo-oligomer. When present, the spacer will usually be at least one or two residues, more usually three to six residues. Alternatively, the CTL peptide may be linked to the T helper peptide without a spacer.

The CTL peptide epitope may be linked to the T helper peptide epitope either directly or via a spacer either at the amino or carboxy terminus of the CTL peptide. The amino terminus of either the immunogenic peptide or the T helper peptide may be acylated. The HTL peptide epitopes used in the invention can be modified in the same manner as CTL peptides. For instance, they may be modified to include D-amino acids or be conjugated to other molecules such as lipids, proteins, sugars and the like.

In certain embodiments, the T helper peptide is one that is recognized by T helper cells present in the majority of the population. This can be accomplished by selecting amino acid sequences that bind to many, most, or all of the HLA class II molecules. These are known as "loosely HLA-restricted" or "promiscuous" T helper sequences. Examples of amino acid sequences that are promiscuous include sequences from antigens such as tetanus toxoid at positions 830-843 (QYIKANSKFIGITE), *Plasmodium falciparum* CS protein at positions 378-398 (DIEKKIAKMEKASSVFNVVNS), and Streptococcus 18kD protein at positions 116 (GAVDSILGGVATYGAA). Other examples include peptides bearing a DR 1-4-7 supermotif, or either of the DR3 motifs.

Alternatively, it is possible to prepare synthetic peptides capable of stimulating T helper lymphocytes, in a loosely HLA-restricted fashion, using amino acid sequences not found in nature (*see, e.g.*, PCT publication WO 95/07707). These synthetic compounds called Pan-DR-binding epitopes (*e.g.*, PADRE™, Epimmune, Inc., San Diego, CA) are designed to most preferrably bind most HLA-DR (human HLA class II) molecules. For instance, a pan-DR-binding epitope peptide having the formula: aKXVWANTLKAAa, where "X" is either cyclohexylalanine, phenylalanine, or tyrosine, and "a" is either D-alanine or L-alanine, has been found to bind to most HLA-DR alleles, and to stimulate the response of T helper lymphocytes from most individuals, regardless of their HLA type. An alternative of a pan-DR binding epitope comprises all "L" natural amino acids and can be provided in the form of nucleic acids that encode the epitope.

HTL peptide epitopes can also be modified to alter their biological properties. For example, peptides comprising HTL epitopes can contain D-amino acids to increase their resistance to proteases and thus extend their serum half-life. Also, the epitope peptides of the invention can be conjugated to other molecules such as lipids, proteins or sugars, or any other synthetic compounds, to increase their biological activity. Specifically, the T helper peptide can be conjugated to one or more palmitic acid chains at either the amino or carboxyl termini.

In some embodiments it may be desirable to include in the pharmaceutical compositions of the invention at least one component which primes cytotoxic T lymphocytes. Lipids have been identified as agents capable of priming CTL *in vivo* against viral antigens. For example, palmitic acid residues can be attached to the ε-and α-amino groups of a lysine residue and then linked, *e.g.*, via one or more linking residues such as Gly, Gly-Gly-, Ser, Ser-Ser, or the like, to an immunogenic peptide. The

lipidated peptide can then be administered either directly in a micelle or particle, incorporated into a liposome, or emulsified in an adjuvant, *e.g.,* incomplete Freund's adjuvant. A particularly effective immunogen comprises palmitic acid attached to ε- and α- amino groups of Lys, which is attached via linkage, *e.g.,* Ser-Ser, to the amino terminus of the immunogenic peptide.

As another example of lipid priming of CTL responses, *E. coli* lipoproteins, such as tripalmitoyl-S-glycerylcysteinlyseryl- serine (P_3CSS) can be used to prime virus specific CTL when covalently attached to an appropriate peptide (*see, e.g.*, Deres, *et al., Nature* 342:561, 1989). Peptides of the invention can be coupled to P_3CSS, for example, and the lipopeptide administered to an individual to specifically prime a CTL response to the target antigen. Moreover, because the induction of neutralizing antibodies can also be primed with P_3CSS-conjugated epitopes, two such compositions can be combined to more effectively elicit both humoral and cell-mediated responses to infection.

As noted herein, additional amino acids can be added to the termini of a peptide to provide for ease of linking peptides one to another, for coupling to a carrier support or larger peptide, for modifying the physical or chemical properties of the peptide or oligopeptide, or the like. Amino acids such as tyrosine, cysteine, lysine, glutamic or aspartic acid, or the like, can be introduced at the C- or N-terminus of the peptide or oligopeptide, particularly class I peptides. However, it is to be noted that modification at the carboxyl terminus of a CTL epitope may, in some cases, alter binding characteristics of the peptide. In addition, the peptide or oligopeptide sequences can differ from the natural sequence by being modified by terminal-NH_2 acylation, *e.g.*, by alkanoyl (C_1-C_{20}) or thioglycolyl acetylation, terminal-carboxyl amidation, *e.g.,* ammonia, methylamine, *etc.* In some instances these modifications may provide sites for linking to a support or other molecule.

IV.L. Administration of Vaccines for Therapeutic or Prophylactic Purposes

The peptides of the present invention and pharmaceutical and vaccine compositions of the invention are useful for administration to mammals, particularly humans, to treat and/or prevent cancer. Vaccine compositions containing the peptides of the invention are administered to a cancer patient or to an individual susceptible to, or otherwise at risk for, cancer to elicit an immune response against TAAs and thus enhance the patient's own immune response capabilities. In therapeutic applications, peptide

and/or nucleic acid compositions are administered to a patient in an amount sufficient to elicit an effective CTL and/or HTL response to the tumor antigen and to cure or at least partially arrest or slow symptoms and/or complications. An amount adequate to accomplish this is defined as "therapeutically effective dose." Amounts effective for this use will depend on, *e.g.*, the particular composition administered, the manner of administration, the stage and severity of the disease being treated, the weight and general state of health of the patient, and the judgment of the prescribing physician.

The vaccine compositions of the invention may also be used purely as prophylactic agents. Generally the dosage for an initial prophylactic immunization generally occurs in a unit dosage range where the lower value is about 1, 5, 50, 500, or 1000 μg and the higher value is about 10,000; 20,000; 30,000; or 50,000 μg. Dosage values for a human typically range from about 500 μg to about 50,000 μg per 70 kilogram patient. This is followed by boosting dosages of between about 1.0 μg to about 50,000 μg of peptide administered at defined intervals from about four weeks to six months after the initial administration of vaccine. The immunogenicity of the vaccine may be assessed by measuring the specific activity of CTL and HTL obtained from a sample of the patient's blood.

As noted above, peptides comprising CTL and/or HTL epitopes of the invention induce immune responses when presented by HLA molecules and contacted with a CTL or HTL specific for an epitope comprised by the peptide. The manner in which the peptide is contacted with the CTL or HTL is not critical to the invention. For instance, the peptide can be contacted with the CTL or HTL either *in vivo* or *in vitro*. If the contacting occurs *in vivo*, the peptide itself can be administered to the patient, or other vehicles, *e.g.*, DNA vectors encoding one or more peptides, viral vectors encoding the peptide(s), liposomes and the like, can be used, as described herein.

When the peptide is contacted *in vitro*, the vaccinating agent can comprise a population of cells, *e.g.*, peptide-pulsed dendritic cells, or TAA-specific CTLs, which have been induced by pulsing antigen-presenting cells *in vitro* with the peptide. Such a cell population is subsequently administered to a patient in a therapeutically effective dose.

For pharmaceutical compositions, the immunogenic peptides of the invention, or DNA encoding them, are generally administered to an individual already diagnosed with cancer. The peptides or DNA encoding them can be administered individually or as fusions of one or more peptide sequences.

For therapeutic use, administration should generally begin at the first diagnosis of cancer. This is followed by boosting doses until at least symptoms are substantially abated and for a period thereafter. The embodiment of the vaccine composition (i.e., including, but not limited to embodiments such as peptide cocktails, polyepitopic polypeptides, minigenes, or TAA-specific CTLs) delivered to the patient may vary according to the stage of the disease. For example, a vaccine comprising TAA-specific CTLs may be more efficacious in killing tumor cells in patients with advanced disease than alternative embodiments.

The vaccine compositions of the invention may also be used therapeutically in combination with treatments such as surgery. An example is a situation in which a patient has undergone surgery to remove a primary tumor and the vaccine is then used to slow or prevent recurrence and/or metastasis.

Where susceptible individuals, *e.g.*, individuals who may be diagnosed as being genetically pre-disposed to developing a particular type of tumor, are identified prior to diagnosis of cancer, the composition can be targeted to them, thus minimizing the need for administration to a larger population.

The dosage for an initial therapeutic immunization generally occurs in a unit dosage range where the lower value is about 1, 5, 50, 500, or 1,000 μg and the higher value is about 10,000; 20,000; 30,000; or 50,000 μg. Dosage values for a human typically range from about 500 μg to about 50,000 μg per 70 kilogram patient. Boosting dosages of between about 1.0 μg to about 50,000 μg of peptide pursuant to a boosting regimen over weeks to months may be administered depending upon the patient's response and condition as determined by measuring the specific activity of CTL and HTL obtained from the patient's blood. The peptides and compositions of the present invention may be employed in serious disease states, that is, life-threatening or potentially life threatening situations. In such cases, as a result of the minimal amounts of extraneous substances and the relative nontoxic nature of the peptides in preferred compositions of the invention, it is possible and may be felt desirable by the treating physician to administer substantial excesses of these peptide compositions relative to these stated dosage amounts.

Thus, for treatment of cancer, a representative dose is in the range disclosed above, namely where the lower value is about 1, 5, 50, 500, or 1,000 μg and the higher value is about 10,000; 20,000; 30,000; or 50,000 μg, preferably from about 500 μg to about 50,000 μg per 70 kilogram patient. Initial doses followed by boosting doses at

established intervals, *e.g.*, from four weeks to six months, may be required, possibly for a prolonged period of time to effectively immunize an individual. Administration should continue until at least clinical symptoms or laboratory tests indicate that the tumor has been eliminated or that the tumor cell burden has been substantially reduced and for a period thereafter. The dosages, routes of administration, and dose schedules are adjusted in accordance with methodologies known in the art.

The pharmaceutical compositions for therapeutic treatment are intended for parenteral, topical, oral, intrathecal, or local administration. Preferably, the pharmaceutical compositions are administered parentally, *e.g.*, intravenously, subcutaneously, intradermally, or intramuscularly. Thus, the invention provides compositions for parenteral administration which comprise a solution of the immunogenic peptides dissolved or suspended in an acceptable carrier, preferably an aqueous carrier. A variety of aqueous carriers may be used, *e.g.*, water, buffered water, 0.8% saline, 0.3% glycine, hyaluronic acid and the like. These compositions may be sterilized by conventional, well known sterilization techniques, or may be sterile filtered. The resulting aqueous solutions may be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile solution prior to administration. The compositions may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions, such as pH-adjusting and buffering agents, tonicity adjusting agents, wetting agents, preservatives, and the like, for example, sodium acetate, sodium lactate, sodium chloride, potassium chloride, calcium chloride, sorbitan monolaurate, triethanolamine oleate, *etc.*

The concentration of peptides of the invention in the pharmaceutical formulations can vary widely, *i.e.*, from less than about 0.1%, usually at or at least about 2% to as much as 20% to 50% or more by weight, and will be selected primarily by fluid volumes, viscosities, *etc.*, in accordance with the particular mode of administration selected.

A human unit dose form of the peptide composition is typically included in a pharmaceutical composition that comprises a human unit dose of an acceptable carrier, preferably an aqueous carrier, and is administered in a volume of fluid that is known by those of skill in the art to be used for administration of such compositions to humans (*see*, *e.g.*, Remington's Pharmaceutical Sciences, 17th Edition, A. Gennaro, Editor, Mack Publishing Co., Easton, Pennsylvania, 1985).

The peptides of the invention may also be administered via liposomes, which serve to target the peptides to a particular tissue, such as lymphoid tissue, or to target

selectively to infected cells, as well as to increase the half-life of the peptide composition. Liposomes include emulsions, foams, micelles, insoluble monolayers, liquid crystals, phospholipid dispersions, lamellar layers and the like. In these preparations, the peptide to be delivered is incorporated as part of a liposome, alone or in conjunction with a molecule which binds to a receptor prevalent among lymphoid cells, such as monoclonal antibodies which bind to the CD45 antigen, or with other therapeutic or immunogenic compositions. Thus, liposomes either filled or decorated with a desired peptide of the invention can be directed to the site of lymphoid cells, where the liposomes then deliver the peptide compositions. Liposomes for use in accordance with the invention are formed from standard vesicle-forming lipids, which generally include neutral and negatively charged phospholipids and a sterol, such as cholesterol. The selection of lipids is generally guided by consideration of, *e.g.,* liposome size, acid lability and stability of the liposomes in the blood stream. A variety of methods are available for preparing liposomes, as described in, *e.g.,* Szoka, *et al., Ann. Rev. Biophys. Bioeng.* 9:467 (1980), and U.S. Patent Nos. 4,235,871, 4,501,728, 4,837,028, and 5,019,369.

For targeting cells of the immune system, a ligand to be incorporated into the liposome can include, *e.g.*, antibodies or fragments thereof specific for cell surface determinants of the desired immune system cells. A liposome suspension containing a peptide may be administered intravenously, locally, topically, *etc.* in a dose which varies according to, *inter alia*, the manner of administration, the peptide being delivered, and the stage of the disease being treated.

For solid compositions, conventional nontoxic solid carriers may be used which include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like. For oral administration, a pharmaceutically acceptable nontoxic composition is formed by incorporating any of the normally employed excipients, such as those carriers previously listed, and generally 10-95% of active ingredient, that is, one or more peptides of the invention, and more preferably at a concentration of 25%-75%.

For aerosol administration, the immunogenic peptides are preferably supplied in finely divided form along with a surfactant and propellant. Typical percentages of peptides are 0.01%-20% by weight, preferably 1%-10%. The surfactant must, of course, be nontoxic, and preferably soluble in the propellant. Representative of such agents are the esters or partial esters of fatty acids containing from 6 to 22 carbon atoms, such as caproic, octanoic, lauric, palmitic, stearic, linoleic, linolenic, olesteric and oleic acids with

an aliphatic polyhydric alcohol or its cyclic anhydride. Mixed esters, such as mixed or natural glycerides may be employed. The surfactant may constitute 0.1%-20% by weight of the composition, preferably 0.25-5%. The balance of the composition is ordinarily propellant. A carrier can also be included, as desired, as with, *e.g.*, lecithin for intranasal delivery.

IV.M. Kits

The peptide and nucleic acid compositions of this invention can be provided in kit form together with instructions for vaccine administration. Typically the kit would include desired peptide compositions in a container, preferably in unit dosage form and instructions for administration. An alternative kit would include a minigene construct with desired nucleic acids of the invention in a container, preferably in unit dosage form together with instructions for administration. Lymphokines such as IL-2 or IL-12 may also be included in the kit. Other kit components that may also be desirable include, for example, a sterile syringe, booster dosages, and other desired excipients.

The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of non-critical parameters that can be changed or modified to yield alternative embodiments in accordance with the invention.

V. EXAMPLES

The following examples illustrate identification, selection, and use of immunogenic Class I and Class II peptide epitopes for inclusion in vaccine compositions.

Example 1. HLA Class I and Class II Binding Assays

The following example of peptide binding to HLA molecules demonstrates quantification of binding affinities of HLA class I and class II peptides. Binding assays can be performed with peptides that are either motif-bearing or not motif-bearing.

Epstein-Barr virus (EBV)-transformed homozygous cell lines, fibroblasts, CIR, or 721.221-transfectants were used as sources of HLA class I molecules. These cells were maintained *in vitro* by culture in RPMI 1640 medium supplemented with 2mM L-glutamine (GIBCO, Grand Island, NY), 50μM 2-ME, 100μg/ml of streptomycin,

100U/ml of penicillin (Irvine Scientific) and 10% heat-inactivated FCS (Irvine Scientific, Santa Ana, CA). Cells were grown in 225-cm^2 tissue culture flasks or, for large-scale cultures, in roller bottle apparatuses. The specific cell lines routinely used for purification of MHC class I and class II molecules are listed in Table XXIV.

Cell lysates were prepared and HLA molecules purified in accordance with disclosed protocols (Sidney *et al.*, *Current Protocols in Immunology* 18.3.1 (1998); Sidney, *et al., J. Immunol.* 154:247 (1995); Sette, *et al., Mol. Immunol.* 31:813 (1994)). Briefly, cells were lysed at a concentration of 10^8 cells/ml in 50 mM Tris-HCl, pH 8.5, containing 1% Nonidet P-40 (Fluka Biochemika, Buchs, Switzerland), 150 mM NaCl, 5 mM EDTA, and 2 mM PMSF. Lysates were cleared of debris and nuclei by centrifugation at 15,000 x g for 30min.

HLA molecules were purified from lysates by affinity chromatography. Lysates prepared as above were passed twice through two pre-columns of inactivated Sepharose CL4-B and protein A-Sepharose. Next, the lysate was passed over a column of Sepharose CL-4B beads coupled to an appropriate antibody. The antibodies used for the extraction of HLA from cell lysates are listed in Table XXV. The anti-HLA column was then washed with 10-column volumes of 10mM Tris-HCL, pH 8.0, in 1% NP-40, PBS, 2-column volumes of PBS, and 2-column volumes of PBS containing 0.4% n-octylglucoside. Finally, MHC molecules were eluted with 50mM diethylamine in 0.15M NaCl containing 0.4% n-octylglucoside, pH 11.5. A 1/25 volume of 2.0M Tris, pH 6.8, was added to the eluate to reduce the pH to ~8.0. Eluates were then concentrated by centrifugation in Centriprep 30 concentrators at 2000 rpm (Amicon, Beverly, MA). Protein content was evaluated by a BCA protein assay (Pierce Chemical Co., Rockford, IL) and confirmed by SDS-PAGE.

A detailed description of the protocol utilized to measure the binding of peptides to Class I and Class II MHC has been published (Sette *et al.*, *Mol. Immunol.* 31:813, 1994; Sidney *et al.*, in *Current Protocols in Immunology*, Margulies, Ed., John Wiley & Sons, New York, Section 18.3, 1998). Briefly, purified MHC molecules (5 to 500nM) were incubated with various unlabeled peptide inhibitors and 1-10nM ^{125}I-radiolabeled probe peptides for 48h in PBS containing 0.05% Nonidet P-40 (NP40) (or 20% w/v digitonin for H-2 IA assays) in the presence of a protease inhibitor cocktail. The final concentrations of protease inhibitors (each from CalBioChem, La Jolla, CA) were 1 mM PMSF, 1.3 nM 1.10 phenanthroline, 73 μM pepstatin A, 8mM EDTA, 6mM N-

ethylmaleimide (for Class II assays), and 200 μM N alpha-p-tosyl-L-lysine chloromethyl ketone (TLCK). All assays were performed at pH 7.0 with the exception of DRB1*0301, which was performed at pH 4.5, and DRB1*1601 (DR2w21β_1) and DRB4*0101 (DRw53), which were performed at pH 5.0. pH was adjusted as described elsewhere (see Sidney *et al.*, in *Current Protocols in Immunology*, Margulies, Ed., John Wiley & Sons, New York, Section 18.3, 1998).

Following incubation, MHC-peptide complexes were separated from free peptide by gel filtration on 7.8 mm x 15 cm TSK200 columns (TosoHaas 16215, Montgomeryville, PA), eluted at 1.2 mls/min with PBS pH 6.5 containing 0.5% NP40 and 0.1% NaN_3. Because the large size of the radiolabeled peptide used for the DRB1*1501 (DR2w2β_1) assay makes separation of bound from unbound peaks more difficult under these conditions, all DRB1*1501 (DR2w2β_1) assays were performed using a 7.8mm x 30cm TSK2000 column eluted at 0.6 mls/min. The eluate from the TSK columns was passed through a Beckman 170 radioisotope detector, and radioactivity was plotted and integrated using a Hewlett-Packard 3396A integrator, and the fraction of peptide bound was determined.

Radiolabeled peptides were iodinated using the chloramine-T method. Representative radiolabeled probe peptides utilized in each assay, and its assay specific IC_{50} nM, are summarized in Tables IV and V. Typically, in preliminary experiments, each MHC preparation was titered in the presence of fixed amounts of radiolabeled peptides to determine the concentration of HLA molecules necessary to bind 10-20% of the total radioactivity. All subsequent inhibition and direct binding assays were performed using these HLA concentrations.

Since under these conditions [label]<[HLA] and $IC_{50} \geq$[HLA], the measured IC_{50} values are reasonable approximations of the true K_D values. Peptide inhibitors are typically tested at concentrations ranging from 120 μg/ml to 1.2 ng/ml, and are tested in two to four completely independent experiments. To allow comparison of the data obtained in different experiments, a relative binding figure is calculated for each peptide by dividing the IC_{50} of a positive control for inhibition by the IC_{50} for each tested peptide (typically unlabeled versions of the radiolabeled probe peptide). For database purposes, and inter-experiment comparisons, relative binding values are compiled. These values can subsequently be converted back into IC_{50} nM values by dividing the IC_{50} nM of the positive controls for inhibition by the relative binding of the peptide of interest. This

method of data compilation has proven to be the most accurate and consistent for comparing peptides that have been tested on different days, or with different lots of purified MHC.

Because the antibody used for HLA-DR purification (LB3.1) is α-chain specific, β_1 molecules are not separated from β_3 (and/or β_4 and β_5) molecules. The β_1 specificity of the binding assay is obvious in the cases of DRB1*0101 (DR1), DRB1*0802 (DR8w2), and DRB1*0803 (DR8w3), where no β_3 is expressed. It has also been demonstrated for DRB1*0301 (DR3) and DRB3*0101 (DR52a), DRB1*0401 (DR4w4), DRB1*0404 (DR4w14), DRB1*0405 (DR4w15), DRB1*1101 (DR5), DRB1*1201 (DR5w12), DRB1*1302 (DR6w19) and DRB1*0701 (DR7). The problem of β chain specificity for DRB1*1501 (DR2w2β_1), DRB5*0101 (DR2w2β_2), DRB1*1601 (DR2w21β_1), DRB5*0201 (DR51Dw21), and DRB4*0101 (DRw53) assays is circumvented by the use of fibroblasts. Development and validation of assays with regard to DRβ molecule specificity have been described previously (*see, e.g.*, Southwood *et al.*, *J. Immunol.* 160:3363-3373, 1998).

Binding assays as outlined above may be used to analyze supermotif and/or motif-bearing epitopes as, for example, described in Example 2.

Example 2. Identification of HLA Supermotif- and Motif-Bearing CTL Candidate Epitopes

Vaccine compositions of the invention may include multiple epitopes that comprise multiple HLA supermotifs or motifs to achieve broad population coverage. This example illustrates the identification of supermotif- and motif-bearing epitopes for the inclusion in such a vaccine composition. Calculation of population coverage is performed using the strategy described below.

Computer searches and algorthims for identification of supermotif and/or motif-bearing epitopes

The searches performed to identify the motif-bearing peptide sequences in Examples 2 and 5 employed protein sequence data for the tumor-associated antigen HER2/neu.

Computer searches for epitopes bearing HLA Class I or Class II supermotifs or motifs were performed as follows. All translated protein sequences were analyzed using

a text string search software program, *e.g.*, MotifSearch 1.4 (D. Brown, San Diego) to identify potential peptide sequences containing appropriate HLA binding motifs; alternative programs are readily produced in accordance with information in the art in view of the motif/supermotif disclosure herein. Furthermore, such calculations can be made mentally. Identified A2-, A3-, and DR-supermotif sequences were scored using polynomial algorithms to predict their capacity to bind to specific HLA-Class I or Class II molecules. These polynomial algorithms take into account both extended and refined motifs (that is, to account for the impact of different amino acids at different positions), and are essentially based on the premise that the overall affinity (or ΔG) of peptide-HLA molecule interactions can be approximated as a linear polynomial function of the type:

$$\text{“}\Delta G\text{”} = a_{1i} \times a_{2i} \times a_{3i} \ldots\ldots \times a_{ni}$$

where a_{ji} is a coefficient which represents the effect of the presence of a given amino acid (j) at a given position (i) along the sequence of a peptide of n amino acids. The crucial assumption of this method is that the effects at each position are essentially independent of each other (i.e., independent binding of individual side-chains). When residue j occurs at position i in the peptide, it is assumed to contribute a constant amount j_i to the free energy of binding of the peptide irrespective of the sequence of the rest of the peptide. This assumption is justified by studies from our laboratories that demonstrated that peptides are bound to MHC and recognized by T cells in essentially an extended conformation (data omitted herein).

The method of derivation of specific algorithm coefficients has been described in Gulukota *et al.*, *J. Mol. Biol.* 267:1258-126, 1997; (*see* also Sidney *et al.*, *Human Immunol.* 45:79-93, 1996; and Southwood *et al.*, *J. Immunol.* 160:3363-3373, 1998). Briefly, for all i positions, anchor and non-anchor alike, the geometric mean of the average relative binding (ARB) of all peptides carrying j is calculated relative to the remainder of the group, and used as the estimate of j_i. For Class II peptides, if multiple alignments are possible, only the highest scoring alignment is utilized, following an iterative procedure. To calculate an algorithm score of a given peptide in a test set, the ARB values corresponding to the sequence of the peptide are multiplied. If this product exceeds a chosen threshold, the peptide is predicted to bind. Appropriate thresholds are chosen as a function of the degree of stringency of prediction desired.

Selection of HLA-A2 supertype cross-reactive peptides

The complete protein sequence from HER2/neu was scanned, utilizing motif identification software, to identify 8-, 9-, 10-, and 11-mer sequences containing the HLA-A2-supermotif main anchor specificity.

A total of 623 HLA-A2 supermotif-positive sequences were identified. Of these, 73 scored positive in the A2 algorithm and the peptides corresponding to the sequences were then synthesized. An additional 90 A2 supermotif-bearing nonamers and decamers were also synthesized. These 163 peptides were then tested for their capacity to bind purified HLA-A*0201 molecules *in vitro* (HLA-A*0201 is considered a prototype A2 supertype molecule). Twenty of the peptides bound A*0201 with IC_{50} values ≤500 nM.

The twenty A*0201-binding peptides were subsequently tested for the capacity to bind to additional A2-supertype molecules (A*0202, A*0203, A*0206, and A*6802). As shown in Table XXVI, 9 of the 20 peptides were found to be A2-supertype cross-reactive binders, binding at least three of the five A2-supertype alleles tested.

Selection of HLA-A3 supermotif-bearing epitopes

The protein sequences scanned above are also examined for the presence of peptides with the HLA-A3-supermotif primary anchors using methodology similar to that performed to identify HLA-A2 supermotif-bearing epitopes.

Peptides corresponding to the supermotif-bearing sequences are then synthesized and tested for binding to HLA-A*0301 and HLA-A*1101 molecules, the two most prevalent A3-supertype alleles. The peptides that are found to bind one of the two alleles with binding affinities of ≤500 nM are then tested for binding cross-reactivity to the other common A3-supertype alleles (A*3101, A*3301, and A*6801) to identify those that can bind at least three of the five HLA-A3-supertype molecules tested.

Selection of HLA-B7 supermotif bearing epitopes

The same target antigen protein sequences are also analyzed to identify HLA-B7-supermotif-bearing sequences. The corresponding peptides are then synthesized and tested for binding to HLA-B*0702, the most common B7-supertype allele (*i.e.*, the prototype B7 supertype allele). Those peptides that bind B*0702 with IC_{50} of ≤500 nM are then tested for binding to other common B7-supertype molecules (B*3501, B*5101,

B*5301, and B*5401) to identify those peptides that are capable of binding to three or more of the five B7-supertype alleles tested.

Selection of A1 and A24 motif-bearing epitopes

To further increase population coverage, HLA-A1 and -A24 epitopes can also be incorporated into potential vaccine constructs. An analysis of the protein sequence data from the target antigens utilized above can also be performed to identify HLA-A1- and A24-motif-containing conserved sequences.

Example 3. Confirmation of Immunogenicity

The nine cross-reactive candidate CTL A2-supermotif-bearing peptides identified in Example 2 were selected for *in vitro* immunogenicity testing. Testing was performed using the following methodology:

Target Cell Lines for Cellular Screening:

The .221A2.1 cell line, produced by transferring the HLA-A2.1 gene into the HLA-A, -B, -C null mutant human B-lymphoblastoid cell line 721.221, was used as the peptide-loaded target to measure activity of HLA-A2.1-restricted CTL. The colon adenocarcinoma cell lines SW403 and HT-29 were obtained from the American Type Culture Collection (ATCC) (Rockville, MD). The cell lines that were obtained from ATCC were maintained under the culture conditions recommended by the supplier. All other cell lines were grown in RPMI-1640 medium supplemented with antibiotics, sodium pyruvate, nonessential amino acids and 10% (v/v) heat inactivated FCS. The colon cancer cells were treated with 100U/ml IFNγ (Genzyme) for 48 hours at 37°C before use as targets in the ^{51}Cr release and *in situ* IFNγ assays.

Primary CTL Induction Cultures:

Generation of Dendritic Cells (DC): PBMCs were thawed in RPMI with 30 μg/ml DNAse, washed twice and resuspended in complete medium (RPMI-1640 plus 5% AB human serum, non-essential amino acids, sodium pyruvate, L-glutamine and penicillin/strpetomycin). The monocytes were purified by plating 10 x 10^6 PBMC/well in a 6-well plate. After 2 hours at 37°C, the non-adherent cells were removed by gently shaking the plates and aspirating the supernatants. The wells were washed a total of three

times with 3 ml RPMI to remove most of the non-adherent and loosely adherent cells. Three ml of complete medium containing 50 ng/ml of GM-CSF and 1,000 U/ml of IL-4 were then added to each well. DC were used for CTL induction cultures following 7 days of culture.

Induction of CTL with DC and Peptide: CD8+ T-cells were isolated by positive selection with Dynal immunomagnetic beads (Dynabeads® M-450) and the detacha-bead® reagent. Typically about 200-250x10^6 PBMC were processed to obtain 24x10^6 $CD8^+$ T-cells (enough for a 48-well plate culture). Briefly, the PBMCs were thawed in RPMI with 30µg/ml DNAse, washed once with PBS containing 1% human AB serum and resuspended in PBS/1% AB serum at a concentration of 20x10^6cells/ml. The magnetic beads were washed 3 times with PBS/AB serum, added to the cells (140µl beads/20x10^6 cells) and incubated for 1 hour at 4°C with continuous mixing. The beads and cells were washed 4x with PBS/AB serum to remove the nonadherent cells and resuspended at 100x10^6 cells/ml (based on the original cell number) in PBS/AB serum containing 100µl/ml detacha-bead® reagent and 30µg/ml DNAse. The mixture is incubated for 1 hour at room temperature with continuous mixing. The beads were washed again with PBS/AB/DNAse to collect the CD8+ T-cells. The DC were collected and centrifuged at 1300 rpm for 5-7 minutes, washed once with PBS with 1% BSA, counted and pulsed with 40µg/ml of peptide at a cell concentration of 1-2x10^6/ml in the presence of 3µg/ml $ß_2$- microglobulin for 4 hours at 20°C. The DC were then irradiated (4,200 rads), washed 1 time with medium and counted again.

Setting up induction cultures: 0.25 ml cytokine-generated DC (@1x10^5 cells/ml) were co-cultured with 0.25ml of CD8+ T-cells (@2x10^6 cell/ml) in each well of a 48-well plate in the presence of 10 ng/ml of IL-7. rHuman IL10 was added the next day at a final concentration of 10 ng/ml and rhuman IL2 was added 48 hours later at 10IU/ml.

Restimulation of the induction cultures with peptide-pulsed adherent cells: Seven and fourteen days after the primary induction the cells were restimulated with peptide-pulsed adherent cells. The PBMCS were thawed and washed twice with RPMI and DNAse. The cells were resuspended at 5x10^6 cells/ml and irradiated at ~4200 rads. The PBMCs were plated at 2x10^6 in 0.5ml complete medium per well and incubated for 2 hours at 37°C. The plates were washed twice with RPMI by tapping the plate gently to remove the nonadherent cells and the adherent cells pulsed with 10µg/ml of peptide in the presence of 3 µg/ml $ß_2$ microglobulin in 0.25ml RPMI/5%AB per well for 2 hours at 37°C. Peptide solution from each well was aspirated and the wells were washed once

with RPMI. Most of the media was aspirated from the induction cultures (CD8+ cells) and brought to 0.5 ml with fresh media. The cells were then transferred to the wells containing the peptide-pulsed adherent cells. Twenty four hours later rhuman IL10 was added at a final concentration of 10ng/ml and rhuman IL2 was added the next day and again 2-3 days later at 50IU/ml (Tsai *et al.*, *Critical Reviews in Immunology* 18(1-2):65-75, 1998). Seven days later the cultures were assayed for CTL activity in a ^{51}Cr release assay. In some experiments the cultures were assayed for peptide-specific recognition in the in situ IFNγ ELISA at the time of the second restimulation followed by assay of endogenous recognition 7 days later. After expansion, activity was measured in both assays for a side by side comparison.

Measurement of CTL lytic activity by ^{51}Cr release.

Seven days after the second restimulation, cytotoxicity was determined in a standard (5hr) ^{51}Cr release assay by assaying individual wells at a single E:T. Peptide-pulsed targets were prepared by incubating the cells with 10μg/ml peptide overnight at 37°C.

Adherent target cells were removed from culture flasks with trypsin-EDTA. Target cells were labelled with 200μCi of ^{51}Cr sodium chromate (Dupont, Wilmington, DE) for 1 hour at 37°C. Labelled target cells are resuspended at 10^6 per ml and diluted 1:10 with K562 cells at a concentration of $3.3x10^6$/ml (an NK-sensitive erythroblastoma cell line used to reduce non-specific lysis). Target cells (100 μl) and 100μl of effectors were plated in 96 well round-bottom plates and incubated for 5 hours at 37°C. At that time, 100 μl of supernatant were collected from each well and percent lysis was determined according to the formula: [(cpm of the test sample- cpm of the spontaneous ^{51}Cr release sample)/(cpm of the maximal ^{51}Cr release sample- cpm of the spontaneous ^{51}Cr release sample)] x 100. Maximum and spontaneous release were determined by incubating the labelled targets with 1% Trition X-100 and media alone, respectively. A positive culture was defined as one in which the specific lysis (sample-background) was 10% or higher in the case of individual wells and was 15% or more at the 2 highest E:T ratios when expanded cultures were assayed.

***In situ* Measurement of Human γIFN Production as an Indicator of Peptide-specific and Endogenous Recognition**

Immulon 2 plates were coated with mouse anti-human IFNγ monoclonal antibody (4 μg/ml 0.1M $NaHCO_3$, pH8.2) overnight at 4°C. The plates were washed with Ca^{2+}, Mg^{2+}-free PBS/0.05% Tween 20 and blocked with PBS/10% FCS for 2 hours, after which the CTLs (100 μl/well) and targets (100 μl/well) were added to each well, leaving empty wells for the standards and blanks (which received media only). The target cells, either peptide-pulsed or endogenous targets, were used at a concentration of $1x10^6$ cells/ml. The plates were incubated for 48 hours at 37°C with 5% CO_2.

Recombinant human IFNγ was added to the standard wells starting at 400 pg or 1200pg/100μl/well and the plate incubated for 2 hours at 37°C. The plates were washed and 100 μl of biotinylated mouse anti-human IFNγ monoclonal antibody (4μg/ml in PBS/3%FCS/0.05% Tween 20) were added and incubated for 2 hours at room temperature. After washing again, 100 μl HRP-streptavidin were added and the plates incubated for 1 hour at room temperature. The plates were then washed 6x with wash buffer, 100μl/well developing solution (TMB 1:1) were added, and the plates allowed to develop for 5-15 minutes. The reaction was stopped with 50 μl/well 1M H_3PO_4 and read at OD450. A culture was considered positive if it measured at least 50 pg of IFNγ/well above background and was twice the background level of expression.

CTL Expansion. Those cultures that demonstrated specific lytic activity against peptide-pulsed targets and/or tumor targets were expanded over a two week period with anti-CD3. Briefly, $5x10^4$ CD8+ cells were added to a T25 flask containing the following: $1x10^6$ irradiated (4,200 rad) PBMC (autologous or allogeneic) per ml, $2x10^5$ irradiated (8,000 rad) EBV- transformed cells per ml, and OKT3 (anti-CD3) at 30ng per ml in RPMI-1640 containing 10% (v/v) human AB serum, non-essential amino acids, sodium pyruvate, 25μM 2-mercaptoethanol, L-glutamine and penicillin/streptomycin. rHuman IL2 was added 24 hours later at a final concentration of 200IU/ml and every 3 days thereafter with fresh media at 50IU/ml. The cells were split if the cell concentration exceeded $1x10^6$/ml and the cultures were assayed between days 13 and 15 at E:T ratios of 30, 10, 3 and 1:1 in the ^{51}Cr release assay or at $1x10^6$/ml in the *in situ* IFNγ assay using the same targets as before the expansion.

Immunogenicity of A2 supermotif-bearing peptides

The 9 A2-supermotif cross-reactive binding peptides were tested in the cellular assay for the ability to induce peptide-specific CTL in normal individuals. In this analysis, a peptide was considered to be an epitope if it induced peptide-specific CTLs in at least 2 donors (unless otherwise noted) and if those CTLs also recognized the endogenously expressed peptide. Of these nine, 2 were able to induce a peptide-specific CTL response in at least 2 normal donors. Further analysis demonstrated that both of these peptides also recognized target cells pulsed with the wild-type peptide and tumor targets that endogenously express HER2/neu (Table XXVII). An additional wild-type peptide, Her2/neu.5 was selected for evaluation based on its A2.1 binding affinity and, although it binds to only 2 HLA-A2 supertype molecules, it was capable of generating a strong CTL response that was both peptide- and tumor-specific.

Immunogenicity was additionally confirmed using PBMCs isolated from cancer patients. Briefly, PBMCs were isolated from two patients with ovarian cancer, re-stimulated with peptide-pulsed monocytes and assayed for the ability to recognize peptide-pulsed target cells as well as transfected cells endogenously expressing the antigen. These data indicated that Her2/neu.435 was recognized in 2 donors as well as Her2/neu.369, Her2/neu.952, and Her2/neu.48. Her2/neu.689 is also an epitope, but not a supertype binder. Of the other peptides tested, Her2/neu.665 and Her2/neu.773 were recognized by CTLs from only one of the two patients and CTLs to Her2/neu.153 and Her2/neu.789 recognized peptide-pulsed targets only.

*Evaluation of A*03/A11 immunogenicity*

HLA-A3 supermotif-bearing cross-reactive binding peptides are also evaluated for immunogenicity using methodology analogous for that used to evaluate the immunogenicity of the HLA-A2 supermotif peptides.

Evaluation of B7 immunogenicity

Immunogenicity screening of the B7-supertype cross-reactive binding peptides identified in Example 2 are evaluated in a manner analogous to the evaluation of A2-and A3-supermotif-bearing peptides.

Example 4. Implementation of the Extended Supermotif to Improve the Binding Capacity of Native Epitopes by Creating Analogs

HLA motifs and supermotifs (comprising primary and/or secondary residues) are useful in the identification and preparation of highly cross-reactive native peptides, as demonstrated herein. Moreover, the definition of HLA motifs and supermotifs also allows one to engineer highly cross-reactive epitopes by identifying residues within a native peptide sequence which can be analogued, or "fixed" to confer upon the peptide certain characteristics, *e.g.* greater cross-reactivity within the group of HLA molecules that comprise a supertype, and/or greater binding affinity for some or all of those HLA molecules. Examples of analog peptides that exhibit modulated binding affinity are set forth in this example.

Analoguing at Primary Anchor Residues

Peptide engineering strategies were implemented to further increase the cross-reactivity of the epitopes identified above. On the basis of the data disclosed, *e.g.*, in related and co-pending U.S.S.N 09/226,775, the main anchors of A2-supermotif-bearing peptides are altered, for example, to introduce a preferred L, I, V, or M at position 2, and I or V at the C-terminus.

Peptides that exhibit at least weak A*0201 binding (IC_{50} of 5000 nM or less), and carrying suboptimal anchor residues at either position 2, the C-terminal position, or both, can be fixed by introducing canonical substitutions (L at position 2 and V at the C-terminus). Those analogued peptides that show at least a three-fold increase in A*0201 binding and bind with an IC_{50} of 500 nM, or less were then tested for A2 cross-reactive binding along with their wild-type (WT) counterparts. Analogued peptides that bind at least three of the five A2 supertype alleles were then selected for cellular screening analysis.

Additionally, the selection of analogs for cellular screening analysis was further restricted by the capacity of the WT parent peptide to bind at least weakly, *i.e.*, bind at an IC_{50} of 5000nM or less, to three of more A2 supertype alleles. The rationale for this requirement is that the WT peptides must be present endogenously in sufficient quantity to be biologically relevant. Analogued peptides have been shown to have increased immunogenicity and cross-reactivity by T cells specific for the WT epitope (*see, e.g.*, Parkhurst *et al.*, *J. Immunol.* 157:2539, 1996; and Pogue *et al.*, *Proc. Natl. Acad. Sci. USA* 92:8166, 1995).

In the cellular screening of these peptide analogs, it is important to demonstrate that analog-specific CTLs are also able to recognize the wild-type peptide and, when possible, tumor targets that endogenously express the epitope.

Of the 20 peptides identified in Example 2 that bound to HLA-A*0201 at a high affinity, 15 carried suboptimal primary anchor residues and met the criterion for analoguing at primary anchor residues by introducing a canonical substitution. Ten analogs of six of the A*0201-binding peptides were created and tested for primary binding to HLA-A*0201 and supertype binding (Table XXII). In 4 of 6 cases, binding to HLA-A*0201 was improved at least three-fold. In 4 cases, crossbinding capability was also improved. In one instance, peptide Her2/neu.153 did not show a three-fold increase in binding to HLA-A*0201, but crossbinding was improved.

Additionally, 22 peptides that weakly bound to HLA-A*0201 that carry suboptimal anchors were also identified and can also be analogued.

Two analogs of Her2/neu.5, two analogs of Her2/neu.369, one version of Her2/neu.952, and one version of Her2/neu.665 were selected for cellular screening studies. As shown in Table XXVIII, both Her2/neu.369L2V9 and V2V9 induced peptide-specific CTLs and those CTLs also recognized the target tumor cells expressing that endogenously express the antigen. Her2neu.5B3V9 and Her2/neu.952L2B7V10 induced peptide-specific CTLs in at least 2 donors, but when the positive cultures were expanded, no wild-type peptide or endogenous recognition was observed.

The Her2/neu.665L2V9 analog exhibited binding to four of the five A2 supertype alleles tested, whereas the wildtype peptide only binds two of the five alleles. In the cellular screening analysis, a strong peptide-specific CTL response was observed. The positive cultures were expanded and assayed for peptide and endogenous recognition. Peptide-specific CTL activity was maintained in some of the cultures, but no corresponding endogenous recognition was observed.

Using methodology similar to that used to develop HLA-A2 analogs, analogs of HLA-A3 and HLA-B7 supermotif-bearing epitopes are also generated. For example, peptides binding at least weakly to 3/5 of the A3-supertype molecules may be engineered at primary anchor residues to possess a preferred residue (V, S, M, or A) at position 2. The analog peptides are then tested for the ability to bind A*03 and A*11 (prototype A3 supertype alleles). Those peptides that demonstrate ≤ 500 nM binding capacity are then tested for A3-supertype cross-reactivity. B7 supermotif-bearing peptides may, for example, be engineered to possess a preferred residue (V, I, L, or F) at the C-terminal

primary anchor position, as demonstrated by Sidney *et al.* (*J. Immunol.* 157:3480-3490, 1996) and tested for binding to B7 supertype alleles.

Analoguing at Secondary Anchor Residues

Moreover, HLA supermotifs are of value in engineering highly cross-reactive peptides and/or peptides that bind HLA molecules with increased affinity by identifying particular residues at secondary anchor positions that are associated with such properties. For example, the binding capacity of a B7 supermotif-bearing peptide representing a discreet single amino acid substitution at position 1 can be analyzed. A peptide can, for example, be analogued to substitute L with F at position 1 and subsequently be evaluated for increased binding affinity/ and or increased cross-reactivity. This procedure will identify analogued peptides with modulated binding affinity.

Engineered analogs with sufficiently improved binding capacity or cross-reactivity are tested for immunogenicity as above.

Other analoguing strategies

Another form of peptide analoguing, unrelated to the anchor positions, involves the substitution of a cysteine with α-amino butyric acid. Due to its chemical nature, cysteine has the propensity to form disulfide bridges and sufficiently alter the peptide structurally so as to reduce binding capacity. Subtitution of α-amino butyric acid for cysteine not only alleviates this problem, but has been shown to improve binding and crossbinding capabilities in some instances (*see, e.g.*, the review by Sette *et al.*, In: Persistent Viral Infections, Eds. R. Ahmed and I. Chen, John Wiley & Sons, England, 1999).

In conclusion, these data demonstrate that by the use of even single amino acid substitutions, it is possible to increase the binding affinity and/or cross-reactivity of peptide ligands for HLA supertype molecules.

Example 5. Identification of peptide epitope sequences with HLA-DR binding motifs

Peptide epitopes bearing an HLA class II supermotif or motif may also be identified as outlined below using methodology similar to that described in Examples 1-3.

Selection of HLA-DR-supermotif-bearing epitopes

To identify HLA class II HTL epitopes, the HER2/neu protein sequence was analyzed for the presence of sequences bearing an HLA-DR-motif or supermotif. Specifically, 15-mer sequences were selected comprising a DR-supermotif, further comprising a 9-mer core, and three-residue N- and C-terminal flanking regions (15 amino acids total).

Protocols for predicting peptide binding to DR molecules have been developed (Southwood *et al.*, *J. Immunol.* 160:3363-3373, 1998). These protocols, specific for individual DR molecules, allow the scoring, and ranking, of 9-mer core regions. Each protocol not only scores peptide sequences for the presence of DR-supermotif primary anchors (i.e., at position 1 and position 6) within a 9-mer core, but additionally evaluates sequences for the presence of secondary anchors. Using allele specific selection tables (see, *e.g.*, Southwood *et al.*, *ibid.*), it has been found that these protocols efficiently select peptide sequences with a high probability of binding a particular DR molecule. Additionally, it has been found that performing these protocols in tandem, specifically those for DR1, DR4w4, and DR7, can efficiently select DR cross-reactive peptides.

The HER2/neu-derived peptides identified above were tested for their binding capacity for various common HLA-DR molecules. All peptides were initially tested for binding to the DR molecules in the primary panel: DR1, DR4w4, and DR7. Peptides binding at least 2 of these 3 DR molecules with an IC_{50} value of 1000 nM or less, were then tested for binding to DR5*0101, DRB1*1501, DRB1*1101, DRB1*0802, and DRB1*1302. Peptides were considered to be cross-reactive DR supertype binders if they bound at an IC_{50} value of 1000 nM or less to at least 5 of the 8 alleles tested.

Following the strategy outlined above, 188 DR supermotif-bearing sequences were identified within the HER2/neu protein sequence. Of those, 41 scored positive in 2 of the 3 combined DR 147 algorithms. These peptides were synthesized and tested for binding to HLA-DRB1*0101, DRB1*0401, DRB1*0701. Of the 41 peptides tested, 18 bound at least 2 of the 3 alleles (Table XXIX).

These 18 peptides were then tested for binding to secondary DR supertype alleles: DRB5*0101, DRB1*1501, DRB1*1101, DRB1*0802, and DRB1*1302. Nine peptides were identified that bound at least 5 of the 8 alleles tested, of which 8 occurred in distinct, non-overlapping regions (Table XXX).

Selection of DR3 motif peptides

Because HLA-DR3 is an allele that is prevalent in Caucasian, Black, and Hispanic populations, DR3 binding capacity is an important criterion in the selection of HTL epitopes. However, data generated previously indicated that DR3 only rarely cross-reacts with other DR alleles (Sidney *et al., J. Immunol.* 149:2634-2640, 1992; Geluk *et al., J. Immunol.* 152:5742-5748, 1994; Southwood *et al., J. Immunol.* 160:3363-3373, 1998). This is not entirely surprising in that the DR3 peptide-binding motif appears to be distinct from the specificity of most other DR alleles. For maximum efficiency in developing vaccine candidates it would be desirable for DR3 motifs to be clustered in proximity with DR supermotif regions. Thus, peptides shown to be candidates may also be assayed for their DR3 binding capacity. However, in view of the distinct binding specificity of the DR3 motif, peptides binding only to DR3 can also be considered as candidates for inclusion in a vaccine formulation.

To efficiently identify peptides that bind DR3, the HER2/neu protein sequence was analyzed for conserved sequences carrying one of the two DR3 specific binding motifs (Table III) reported by Geluk *et al.* (*J. Immunol.* 152:5742-5748, 1994). Forty-six motif-positive peptides were identified. The corresponding peptides were then synthesized and tested for the ability to bind DR3 with an affinity of 1000 nM or better, *i.e.*, less than 1000 nM. Seven peptides were found that met this binding criterion (Table XXXI), and thereby qualify as HLA class II high affinity binders.

Additionally, the 7 DR3 binders were tested for binding to the DR supertype alleles (Table XXXII). Four of the seven DR3 binders bound at least 3 other DR alleles, and one peptide, Her2/neu.886, was a cross-reactive supertype binder as well. Conversely, the DR supertype cross-reactive binding peptides were also tested for DR3 binding capacity. The cross-reactive DR supermotif-bearing peptides showed little capacity to bind DR3 molecules (Table XXXII).

DR3 binding epitopes identified in this manner may then be included in vaccine compositions with DR supermotif-bearing peptide epitopes.

In summary, 8 DR supertype cross-reactive binding peptides and 7 DR3 binding peptides were identified from the HER2/neu protein sequence, with one peptide shared between the two motifs. Of these, 5 DR supertype and 5 DR3-binding peptides were located in the intracellular domain.

Similarly to the case of HLA class I motif-bearing peptides, the class II motif-bearing peptides may be analogued to improve affinity or cross-reactivity. For example,

aspartic acid at position 4 of the 9-mer core sequence is an optimal residue for DR3 binding, and substitution for that residue may improve DR 3 binding.

Example 6. Immunogenicity of HTL epitopes

This example determines immunogenic DR supermotif- and DR3 motif-bearing epitopes among those identified using the methodology in Example 5. Immunogenicity of HTL epitopes are evaluated in a manner analogous to the determination of immunogenicity of CTL epitopes by assessing the ability to stimulate HTL responses and/or by using appropriate transgenic mouse models. Immunogenicity is determined by screening for: 1.) *in vitro* primary induction using normal PBMC or 2.) recall responses from cancer patient PBMCs.

Example 7. Calculation of phenotypic frequencies of HLA-supertypes in various ethnic backgrounds to determine breadth of population coverage

This example illustrates the assessment of the breadth of population coverage of a vaccine composition comprised of multiple epitopes comprising multiple supermotifs and/or motifs.

In order to analyze population coverage, gene frequencies of HLA alleles were determined. Gene frequencies for each HLA allele were calculated from antigen or allele frequencies utilizing the binomial distribution formulae gf=1-(SQRT(1-af)) (see, *e.g.*, Sidney *et al.*, *Human Immunol.* 45:79-93, 1996). To obtain overall phenotypic frequencies, cumulative gene frequencies were calculated, and the cumulative antigen frequencies derived by the use of the inverse formula [af=1-(1-Cgf)^2].

Where frequency data was not available at the level of DNA typing, correspondence to the serologically defined antigen frequencies was assumed. To obtain total potential supertype population coverage no linkage disequilibrium was assumed, and only alleles confirmed to belong to each of the supertypes were included (minimal estimates). Estimates of total potential coverage achieved by inter-loci combinations were made by adding to the A coverage the proportion of the non-A covered population that could be expected to be covered by the B alleles considered (*e.g.*, total=A+B*(1-A)). Confirmed members of the A3-like supertype are A3, A11, A31, A*3301, and A*6801. Although the A3-like supertype may also include A34, A66, and A*7401, these alleles were not included in overall frequency calculations. Likewise, confirmed members of the A2-like supertype family are A*0201, A*0202, A*0203, A*0204, A*0205, A*0206,

A*0207, A*6802, and A*6901. Finally, the B7-like supertype-confirmed alleles are: B7, B*3501-03, B51, B*5301, B*5401, B*5501-2, B*5601, B*6701, and B*7801 (potentially also B*1401, B*3504-06, B*4201, and B*5602).

Population coverage achieved by combining the A2-, A3- and B7-supertypes is approximately 86% in five major ethnic groups (see Table XXI). Coverage may be extended by including peptides bearing the A1 and A24 motifs. On average, A1 is present in 12% and A24 in 29% of the population across five different major ethnic groups (Caucasian, North American Black, Chinese, Japanese, and Hispanic). Together, these alleles are represented with an average frequency of 39% in these same ethnic populations. The total coverage across the major ethnicities when A1 and A24 are combined with the coverage of the A2-, A3- and B7-supertype alleles is >95%. An analogous approach can be used to estimate population coverage achieved with combinations of class II motif-bearing epitopes.

Example 8. Recognition Of Generation Of Endogenous Processed Antigens After Priming

This example determines that CTL induced by native or analogued peptide epitopes identified and selected as described in Examples 1-6 recognize endogenously synthesized, *i.e.*, native antigens, using a transgenic mouse model.

Effector cells isolated from transgenic mice that are immunized with peptide epitopes (as described, e.g., in Wentworth et al., *Mol. Immunol.* 32:603, 1995), for example HLA-A2 supermotif-bearing epitopes, are re-stimulated *in vitro* using peptide-coated stimulator cells. Six days later, effector cells are assayed for cytotoxicity and the cell lines that contain peptide-specific cytotoxic activity are further re-stimulated. An additional six days later, these cell lines are tested for cytotoxic activity on ^{51}Cr labeled Jurkat-A2.1/K^b target cells in the absence or presence of peptide, and also tested on ^{51}Cr labeled target cells bearing the endogenously synthesized antigen, *i.e.* cells that are stably transfected with TAA expression vectors.

The result will demonstrate that CTL lines obtained from animals primed with peptide epitope recognize endogenously synthesized antigen. The choice of transgenic mouse model to be used for such an analysis depends upon the epitope(s) that is being evaluated. In addition to HLA-A*0201/K^b transgenic mice, several other transgenic mouse models including mice with human A11, which may also be used to evaluate A3 epitopes, and B7 alleles have been characterized and others (*e.g.*, transgenic mice for

HLA-A1 and A24) are being developed. HLA-DR1 and HLA-DR3 mouse models have also been developed, which may be used to evaluate HTL epitopes.

Example 9. Activity Of CTL-HTL Conjugated Epitopes In Transgenic Mice

This example illustrates the induction of CTLs and HTLs in transgenic mice by use of a tumor associated antigen CTL/HTL peptide conjugate whereby the vaccine composition comprises peptides to be administered to a cancer patient. The peptide composition can comprise multiple CTL and/or HTL epitopes and further, can comprise epitopes selected from multiple-tumor associated antigens. The epitopes are identified using methodology as described in Examples 1-6 This analysis demonstrates the enhanced immunogenicity that can be achieved by inclusion of one or more HTL epitopes in a vaccine composition. Such a peptide composition can comprise an HTL epitope conjugated to a preferred CTL epitope containing, for example, at least one CTL epitope selected from Tables XXII, XXVI, XXVII, or other analogs of that epitope. The HTL epitope is, for example, selected from Table XXXII. The peptides may be lipidated, if desired.

Immunization procedures: Immunization of transgenic mice is performed as described (Alexander *et al.*, *J. Immunol.* 159:4753-4761, 1997). For example, A2/K^b mice, which are transgenic for the human HLA A2.1 allele and are useful for the assessment of the immunogenicity of HLA-A*0201 motif- or HLA-A2 supermotif-bearing epitopes, are primed subcutaneously (base of the tail) with 0.1 ml of peptide conjugate formulated in saline, or DMSO/saline. Seven days after priming, splenocytes obtained from these animals are restimulated with syngenic irradiated LPS-activated lymphoblasts coated with peptide.

The target cells for peptide-specific cytotoxicity assays are Jurkat cells transfected with the HLA-A2.1/K^b chimeric gene (*e.g.*, Vitiello *et al.*, *J. Exp. Med.* 173:1007, 1991).

In vitro CTL activation: One week after priming, spleen cells ($30x10^6$ cells/flask) are co-cultured at 37°C with syngeneic, irradiated (3000 rads), peptide coated lymphoblasts ($10x10^6$ cells/flask) in 10 ml of culture medium/T25 flask. After six days, effector cells are harvested and assayed for cytotoxic activity.

Assay for cytotoxic activity: Target cells (1.0 to $1.5x10^6$) are incubated at 37°C in the presence of 200 µl of ^{51}Cr. After 60 minutes, cells are washed three times and resuspended in medium. Peptide is added where required at a concentration of 1 µg/ml. For the assay, 10^4 ^{51}Cr-labeled target cells are added to different concentrations of

effector cells (final volume of 200 µl) in U-bottom 96-well plates. After a 6 hour incubation period at 37°C, a 0.1 ml aliquot of supernatant is removed from each well and radioactivity is determined in a Micromedic automatic gamma counter. The percent specific lysis is determined by the formula: percent specific release = 100 x (experimental release - spontaneous release)/(maximum release - spontaneous release). To facilitate comparison between separate CTL assays run under the same conditions, % ^{51}Cr release data is expressed as lytic units/10^6 cells. One lytic unit is arbitrarily defined as the number of effector cells required to achieve 30% lysis of 10,000 target cells in a 6 hour ^{51}Cr release assay. To obtain specific lytic units/10^6, the lytic units/10^6 obtained in the absence of peptide is subtracted from the lytic units/10^6 obtained in the presence of peptide. For example, if 30% ^{51}Cr release is obtained at the effector (E): target (T) ratio of 50:1 (i.e., $5x10^5$ effector cells for 10,000 targets) in the absence of peptide and 5:1 (i.e., $5x10^4$ effector cells for 10,000 targets) in the presence of peptide, the specific lytic units would be: $[(1/50,000)-(1/500,000)] \times 10^6 = 18$ LU.

The results are analyzed to assess the magnitude of the CTL responses of animals injected with the immunogenic CTL/HTL conjugate vaccine preparation. The magnitude and frequency of the response can also be compared to the the CTL response achieved using the CTL epitopes by themselves. Analyses similar to this may be performed to evaluate the immunogenicity of peptide conjugates containing multiple CTL epitopes and/or multiple HTL epitopes. In accordance with these procedures it is found that a CTL response is induced, and concomitantly that an HTL response is induced upon administration of such compositions.

Example 10. Selection of CTL and HTL epitopes for inclusion in a cancer vaccine.

This example illustrates the procedure for the selection of peptide epitopes for vaccine compositions of the invention. The peptides in the composition may be in the form of a nucleic acid sequence, either single or one or more sequences (*i.e.*, minigene) that encodes peptide(s), or may be single and/or polyepitopic peptides.

The following principles are utilized when selecting an array of epitopes for inclusion in a vaccine composition. Each of the following principles are balanced in order to make the selection.

1.) Epitopes are selected which, upon administration, mimic immune responses that have been observed to be correlated with tumor clearance. For HLA Class

I this includes 3-4 epitopes that come from at least one TAA. For HLA Class II a similar rationale is employed; again 3-4 epitopes are selected from at least one TAA (*see e.g.*, Rosenberg *et al.*, *Science* 278:1447-1450). Epitopes from one TAA may be used in combination with epitopes from one or more additional TAAs to produce a vaccine that targets tumors with varying expression patterns of frequently-expressed TAAs as described, *e.g.*, in Example 15.

2.) Epitopes are selected that have the requisite binding affinity established to be correlated with immunogenicity: for HLA Class I an IC_{50} of 500 nM or less, or for Class II an IC_{50} of 1000 nM or less.

3.) Sufficient supermotif bearing peptides, or a sufficient array of allele-specific motif bearing peptides, are selected to give broad population coverage. For example, epitopes are selected to provide at least 80% population coverage. A Monte Carlo analysis, a statistical evaluation known in the art and discussed herein, can be employed to assess breadth, or redundancy, of population coverage.

4.) When selecting epitopes from cancer-related antigens it is often preferred to select analogs because the patient may have developed tolerance to the native epitope. When selecting epitopes for infectious disease-related antigens it is preferable to select either native or analoged epitopes. Of relevance for infectious disease vaccines (but for cancer-related vaccines as well), are epitopes referred to as "nested epitopes." Nested epitopes occur where at least two epitopes overlap in a given peptide sequence. A peptide comprising "transcendent nested epitopes" is a peptide that has both HLA class I and HLA class II epitopes in it.

When providing nested epitopes, a sequence that has the greatest number of epitopes per provided sequence is provided. A limitation on this principle is to avoid providing a peptide that is any longer than the amino terminus of the amino terminal epitope and the carboxyl terminus of the carboxyl terminal epitope in the peptide. When providing a longer peptide sequence, such as a sequence comprising nested epitopes, the sequence is screened in order to insure that it does not have pathological or other deleterious biological properties.

5.) When creating a minigene, as disclosed in greater detail in Example 11, an objective is to generate the smallest peptide possible that encompasses the epitopes of interest. The principles employed are similar, if not the same as those employed when selecting a peptide comprising nested epitopes. Additionally, however, upon determination of the nucleic acid sequence to be provided as a minigene, the peptide

sequence encoded thereby is analyzed to determine whether any "junctional epitopes" have been created. A junctional epitope is a potential HLA binding epitope, as predicted, *e.g.*, by motif analysis. Junctional epitopes are generally to be avoided because the recipient may bind to an HLA molecule and generate an immune response to that epitope, which is not present in a native protein sequence. Of particular concern is a junctional epitope that is a "dominant epitope." A dominant epitope may lead to such a zealous response that immune responses to other epitopes are diminished or suppressed.

Peptide epitopes for inclusion in vaccine compositions are, for example, selected from those listed in Tables XXII, XXVI, XXVII, and XXXII. A vaccine composition comprised of selected peptides, when administered, is safe, efficacious, and elicits an immune response that results in tumor cell killing and reduction of tumor size or mass.

Example 11. Construction of Minigene Multi-Epitope DNA Plasmids

This example provides general guidance for the construction of a minigene expression plasmid. Minigene plasmids may, of course, contain various configurations of CTL and/or HTL epitopes or epitope analogs as described herein. Expression plasmids have been constructed and evaluated as described, for example, in co-pending U.S.S.N. 09/311,784 filed 5/13/99.

A minigene expression plasmid may include multiple CTL and HTL peptide epitopes. In the present example, HLA-A2, -A3, -B7 supermotif-bearing peptide epitopes and HLA-A1 and -A24 motif-bearing peptide epitopes are used in conjunction with DR supermotif-bearing epitopes and/or DR3 epitopes. Preferred epitopes are identified, for example, in Tables XXII, XXIII, XXVI-XXVIII, and XXXII. HLA class I supermotif or motif-bearing peptide epitopes derived from multiple TAAs are selected such that multiple supermotifs/motifs are represented to ensure broad population coverage. Similarly, HLA class II epitopes are selected from multiple tumor antigens to provide broad population coverage, *i.e.* both HLA DR-1-4-7 supermotif-bearing epitopes and HLA DR-3 motif-bearing epitopes are selected for inclusion in the minigene construct. The selected CTL and HTL epitopes are then incorporated into a minigene for expression in an expression vector.

This example illustrates the methods to be used for construction of such a minigene-bearing expression plasmid. Other expression vectors that may be used for minigene compositions are available and known to those of skill in the art.

The minigene DNA plasmid contains a consensus Kozak sequence and a consensus murine kappa Ig-light chain signal sequence followed by CTL and/or HTL epitopes selected in accordance with principles disclosed herein. The sequence encodes an open reading frame fused to the Myc and His antibody epitope tag coded for by the pcDNA 3.1 Myc-His vector.

Overlapping oligonucleotides, for example eight oligonucleotides, averaging approximately 70 nucleotides in length with 15 nucleotide overlaps, are synthesized and HPLC-purified. The oligonucleotides encode the selected peptide epitopes as well as appropriate linker nucleotides, Kozak sequence, and signal sequence. The final multiepitope minigene is assembled by extending the overlapping oligonucleotides in three sets of reactions using PCR. A Perkin/Elmer 9600 PCR machine is used and a total of 30 cycles are performed using the following conditions: 95°C for 15 sec, annealing temperature (5° below the lowest calculated Tm of each primer pair) for 30 sec, and 72°C for 1 min.

For the first PCR reaction, 5 μg of each of two oligonucleotides are annealed and extended: Oligonucleotides 1+2, 3+4, 5+6, and 7+8 are combined in 100 μl reactions containing *Pfu* polymerase buffer (1x= 10 mM KCL, 10 mM $(NH_4)_2SO_4$, 20 mM Tris-chloride, pH 8.75, 2 mM $MgSO_4$, 0.1% Triton X-100, 100 μg/ml BSA), 0.25 mM each dNTP, and 2.5 U of *Pfu* polymerase. The full-length dimer products are gel-purified, and two reactions containing the product of 1+2 and 3+4, and the product of 5+6 and 7+8 are mixed, annealed, and extended for 10 cycles. Half of the two reactions are then mixed, and 5 cycles of annealing and extension carried out before flanking primers are added to amplify the full length product for 25 additional cycles. The full-length product is gel-purified and cloned into pCR-blunt (Invitrogen) and individual clones are screened by sequencing.

Example 12. The plasmid construct and the degree to which it induces immunogenicity.

The degree to which the plasmid construct prepared using the methodology outlined in Example 11 is able to induce immunogenicity is evaluated through *in vivo* injections into mice and subsequent *in vitro* assessment of CTL and HTL activity, which are analysed using cytotoxicity and proliferation assays, respectively, as detailed *e.g.*, in U.S.S.N. 09/311,784 filed 5/13/99 and Alexander *et al.*, *Immunity* 1:751-761, 1994.

Alternatively, plasmid constructs can be evaluated *in vitro* by testing for epitope presentation by APC following transduction or transfection of the APC with an epitope-

expressing nucleic acid construct. Such a study determines "antigenicity" and allows the use of human APC. The assay determines the ability of the epitope to be presented by the APC in a context that is recognized by a T cell by quantifying the density of epitope-HLA class I complexes on the cell surface. Quantitation can be performed by directly measuring the amount of peptide eluted from the APC (*see, e.g.*, Sijts *et al.*, *J. Immunol.* 156:683-692, 1996; Demotz *et al.*, *Nature* 342:682-684, 1989); or the number of peptide-HLA class I complexes can be estimated by measuring the amount of lysis or lymphokine release induced by infected or transfected target cells, and then determining the concentration of peptide necessary to obtained equivalent levels of lysis or lymphokine release (*see, e.g.*, Kageyama *et al.*, *J. Immunol.* 154:567-576, 1995).

To assess the capacity of the pMin minigene construct (*e.g.*, a pMin minigene construct generated as decribed in U.S.S.N. 09/311,784) to induce CTLs *in vivo*, HLA-A11/K^b transgenic mice, for example, are immunized intramuscularly with 100 μg of naked cDNA. As a means of comparing the level of CTLs induced by cDNA immunization, a control group of animals is also immunized with an actual peptide composition that comprises multiple epitopes synthesized as a single polypeptide as they would be encoded by the minigene.

Splenocytes from immunized animals are stimulated twice with each of the respective compositions (peptide epitopes encoded in the minigene or the polyepitopic peptide), then assayed for peptide-specific cytotoxic activity in a ^{51}Cr release assay. The results indicate the magnitude of the CTL response directed against the A3-restricted epitope, thus indicating the *in vivo* immunogenicity of the minigene vaccine and polyepitopic vaccine. It is, therefore, found that the minigene elicits immune responses directed toward the HLA-A3 supermotif peptide epitopes as does the polyepitopic peptide vaccine. A similar analysis is also performed using other HLA-A2 and HLA-B7 transgenic mouse models to assess CTL induction by HLA-A2 and HLA-B7 motif or supermotif epitopes.

To assess the capacity of a class II epitope encoding minigene to induce HTLs *in vivo*, I-A^b restricted mice, for example, are immunized intramuscularly with 100 μg of plasmid DNA. As a means of comparing the level of HTLs induced by DNA immunization, a group of control animals is also immunized with an actual peptide composition emulsified in complete Freund's adjuvant. CD4+ T cells, *i.e.* HTLs, are purified from splenocytes of immunized animals and stimulated with each of the

respective compositions (peptides encoded in the minigene). The HTL response is measured using a ^{3}H-thymidine incorporation proliferation assay, (*see, e.g.*, Alexander et al. Immunity 1:751-761, 1994). The results indicate the magnitude of the HTL response, thus demonstrating the *in vivo* immunogenicity of the minigene.

DNA minigenes, constructed as described in Example 11, may also be evaluated as a vaccine in combination with a boosting agent using a prime boost protocol. The boosting agent may consist of recombinant protein (*e.g.*, Barnett *et al.*, *Aids Res. and Human Retroviruses* 14, Supplement 3:S299-S309, 1998) or recombinant vaccinia, for example, expressing a minigene or DNA encoding the complete protein of interest (*see, e.g.*, Hanke *et al.*, *Vaccine* 16:439-445, 1998; Sedegah *et al.*, *Proc. Natl. Acad. Sci USA* 95:7648-53, 1998; Hanke and McMichael, *Immunol. Letters* 66:177-181, 1999; and Robinson *et al.*, *Nature Med.* 5:526-34, 1999).

For example, the efficacy of the DNA minigene may be evaluated in transgenic mice. In this example, A2.1/K^{b} transgenic mice are immunized IM with 100 μg of the DNA minigene encoding the immunogenic peptides. After an incubation period (ranging from 3-9 weeks), the mice are boosted IP with 10^{7} pfu/mouse of a recombinant vaccinia virus expressing the same sequence encoded by the DNA minigene. Control mice are immunized with 100 μg of DNA or recombinant vaccinia without the minigene sequence, or with DNA encoding the minigene, but without the vaccinia boost. After an additional incubation period of two weeks, splenocytes from the mice are immediately assayed for peptide-specific activity in an ELISPOT assay. Additionally, splenocytes are stimulated *in vitro* with the A2-restricted peptide epitopes encoded in the minigene and recombinant vaccinia, then assayed for peptide-specific activity in an IFN-γ ELISA. It is found that the minigene utilized in a prime-boost mode elicits greater immune responses toward the HLA-A2 supermotif peptides than with DNA alone. Such an analysis is also performed using other HLA-A11 and HLA-B7 transgenic mouse models to assess CTL induction by HLA-A3 and HLA-B7 motif or supermotif epitopes.

Example 13. Peptide Composition for Prophylactic Uses

Vaccine compositions of the present invention are used to prevent cancer in persons who are at risk for developing a tumor. For example, a polyepitopic peptide epitope composition (or a nucleic acid comprising the same) containing multiple CTL and HTL epitopes such as those selected in Examples 9 and/or 10, which are also selected to

target greater than 80% of the population, is administered to an individual at risk for a cancer, *e.g.*, breast cancer. The composition is provided as a single polypeptide that encompasses multiple epitopes. The vaccine is administered in an aqueous carrier comprised of Freunds Incomplete Adjuvant. The dose of peptide for the initial immunization is from about 1 to about 50,000 μg, generally 100-5,000 μg, for a 70 kg patient. The initial administration of vaccine is followed by booster dosages at 4 weeks followed by evaluation of the magnitude of the immune response in the patient, by techniques that determine the presence of epitope-specific CTL populations in a PBMC sample. Additional booster doses are administered as required. The composition is found to be both safe and efficacious as a prophylaxis against cancer.

Alternatively, the polyepitopic peptide composition can be administered as a nucleic acid in accordance with methodologies known in the art and disclosed herein.

Example 14. Polyepitopic Vaccine Compositions Derived from Native TAA Sequences

A native TAA polyprotein sequence is screened, preferably using computer algorithms defined for each class I and/or class II supermotif or motif, to identify "relatively short" regions of the polyprotein that comprise multiple epitopes and is preferably less in length than an entire native antigen. This relatively short sequence that contains multiple distinct, even overlapping, epitopes is selected and used to generate a minigene construct. The construct is engineered to express the peptide, which corresponds to the native protein sequence. The "relatively short" peptide is generally less than 1000, 500, or 250 amino acids in length, often less than 100 amino acids in length, preferably less than 75 amino acids in length, and more preferably less than 50 amino acids in length. The protein sequence of the vaccine composition is selected because it has maximal number of epitopes contained within the sequence, *i.e.*, it has a high concentration of epitopes. As noted herein, epitope motifs may be nested or overlapping (*i.e.*, frame shifted relative to one another). For example, with frame shifted overlapping epitopes, two 9-mer epitopes and one 10-mer epitope can be present in a 10 amino acid peptide. Such a vaccine composition is administered for therapeutic or prophylactic purposes.

The vaccine composition will preferably include, for example, three CTL epitopes and at least one HTL epitope from TAAs. This polyepitopic native sequence is administered either as a peptide or as a nucleic acid sequence which encodes the peptide. Alternatively, an analog can be made of this native sequence, whereby one or more of the

epitopes comprise substitutions that alter the cross-reactivity and/or binding affinity properties of the polyepitopic peptide.

The embodiment of this example provides for the possibility that an as yet undiscovered aspect of immune system processing will apply to the native nested sequence and thereby facilitate the production of therapeutic or prophylactic immune response-inducing vaccine compositions. Additionally such an embodiment provides for the possibility of motif-bearing epitopes for an HLA makeup that is presently unknown. Furthermore, this embodiment (absent analogs) directs the immune response to multiple peptide sequences that are actually present in native TAAs thus avoiding the need to evaluate any junctional epitopes. Lastly, the embodiment provides an economy of scale when producing nucleic acid vaccine compositions.

Related to this embodiment, computer programs can be derived in accordance with principles in the art, which identify in a target sequence, the greatest number of epitopes per sequence length.

Example 15. Polyepitopic Vaccine Compositions Directed To Multiple Tumors

The HER2/neu peptide epitopes of the present invention are used in conjunction with peptide epitopes from other target tumor antigens to create a vaccine composition that is useful for the treatment of various types of tumors. For example, a set of TAA epitopes can be selected that allows the targeting of most common epithelial tumors (*see, e.g.*, Kawashima *et al.*, *Hum. Immunol.* 59:1-14, 1998). Such a composition includes epitopes from CEA, HER-2/neu, and MAGE2/3, all of which are expressed to appreciable degrees (20-60%) in frequently found tumors such as lung, breast, and gastrointestinal tumors.

The composition can be provided as a single polypeptide that incorporates the multiple epitopes from the various TAAs, or can be administered as a composition comprising one or more discrete epitopes. Alternatively, the vaccine can be administered as a minigene construct or as dendritic cells which have been loaded with the peptide epitopes *in vitro*.

Targeting multiple tumor antigens is also important to provide coverage of a large fraction of tumors of any particular type. A single TAA is rarely expressed in the majority of tumors of a given type. For example, approximately 50% of breast tumors express CEA, 20% express MAGE3, and 30% express HER-2/neu. Thus, the use of a single antigen for immunotherapy would offer only limited patient coverage. The

combination of the three TAAs, however, would address approximately 70% of breast tumors. A vaccine composition comprising epitopes from multiple tumor antigens also reduces the potential for escape mutants due to loss of expression of an individual tumor antigen.

Example 16. Use of peptides to evaluate an immune response

Peptides of the invention may be used to analyze an immune response for the presence of specific CTL or HTL populations directed to a TAA. Such an analysis may be performed using multimeric complexes as described, *e.g.*, by Ogg *et al., Science* 279:2103-2106, 1998 and Greten *et al., Proc. Natl. Acad. Sci. USA* 95:7568-7573, 1998. In the following example, peptides in accordance with the invention are used as a reagent for diagnostic or prognostic purposes, not as an immunogen.

In this example, highly sensitive human leukocyte antigen tetrameric complexes ("tetramers") are used for a cross-sectional analysis of, for example, tumor-associated antigen HLA-A*0201-specific CTL frequencies from HLA A*0201-positive individuals at different stages of disease or following immunization using a TAA peptide containing an A*0201 motif. Tetrameric complexes are synthesized as described (Musey *et al., N. Engl. J. Med.* 337:1267, 1997). Briefly, purified HLA heavy chain (A*0201 in this example) and β2-microglobulin are synthesized by means of a prokaryotic expression system. The heavy chain is modified by deletion of the transmembrane-cytosolic tail and COOH-terminal addition of a sequence containing a BirA enzymatic biotinylation site. The heavy chain, β2-microglobulin, and peptide are refolded by dilution. The 45-kD refolded product is isolated by fast protein liquid chromatography and then biotinylated by BirA in the presence of biotin (Sigma, St. Louis, Missouri), adenosine 5'triphosphate and magnesium. Streptavidin-phycoerythrin conjugate is added in a 1:4 molar ratio, and the tetrameric product is concentrated to 1 mg/ml. The resulting product is referred to as tetramer-phycoerythrin.

For the analysis of patient blood samples, approximately one million PBMCs are centrifuged at 300g for 5 minutes and resuspended in 50 μl of cold phosphate-buffered saline. Tri-color analysis is performed with the tetramer-phycoerythrin, along with anti-CD8-Tricolor, and anti-CD38. The PBMCs are incubated with tetramer and antibodies on ice for 30 to 60 min and then washed twice before formaldehyde fixation. Gates are applied to contain >99.98% of control samples. Controls for the tetramers include both

A*0201-negative individuals and A*0201-positive uninfected donors. The percentage of cells stained with the tetramer is then determined by flow cytometry. The results indicate the number of cells in the PBMC sample that contain epitope-restricted CTLs, thereby readily indicating the extent of immune response to the TAA epitope, and thus the stage of tumor progression or exposure to a vaccine that elicits a protective or therapeutic response.

Example 17. Use of Peptide Epitopes to Evaluate Recall Responses

The peptide epitopes of the invention are used as reagents to evaluate T cell responses, such as acute or recall responses, in patients. Such an analysis may be performed on patients who are in remission, have a tumor, or who have been vaccinated with a TAA vaccine.

For example, the class I restricted CTL response of persons who have been vaccinated may be analyzed. The vaccine may be any TAA vaccine. PBMC are collected from vaccinated individuals and HLA typed. Appropriate peptide epitopes of the invention that, optimally, bear supermotifs to provide cross-reactivity with multiple HLA supertype family members, are then used for analysis of samples derived from individuals who bear that HLA type.

PBMC from vaccinated individuals are separated on Ficoll-Histopaque density gradients (Sigma Chemical Co., St. Louis, MO), washed three times in HBSS (GIBCO Laboratories), resuspended in RPMI-1640 (GIBCO Laboratories) supplemented with L-glutamine (2mM), penicillin (50U/ml), streptomycin (50 μg/ml), and Hepes (10mM) containing 10% heat-inactivated human AB serum (complete RPMI) and plated using microculture formats. A synthetic peptide comprising an epitope of the invention is added at 10 μg/ml to each well and HBV core 128-140 epitope is added at 1 μg/ml to each well as a source of T cell help during the first week of stimulation.

In the microculture format, 4 x 10^5 PBMC are stimulated with peptide in 8 replicate cultures in 96-well round bottom plate in 100 μl/well of complete RPMI. On days 3 and 10, 100 μl of complete RPMI and 20 U/ml final concentration of rIL-2 are added to each well. On day 7 the cultures are transferred into a 96-well flat-bottom plate and restimulated with peptide, rIL-2 and 10^5 irradiated (3,000 rad) autologous feeder cells. The cultures are tested for cytotoxic activity on day 14. A positive CTL response requires two or more of the eight replicate cultures to display greater than 10% specific

^{51}Cr release, based on comparison with uninfected control subjects as previously described (Rehermann, *et al., Nature Med.* 2:1104,1108, 1996; Rehermann *et al., J. Clin. Invest.* 97:1655-1665, 1996; and Rehermann *et al. J. Clin. Invest.* 98:1432-1440, 1996).

Target cell lines are autologous and allogeneic EBV-transformed B-LCL that are either purchased from the American Society for Histocompatibility and Immunogenetics (ASHI, Boston, MA) or established from the pool of patients as described (Guilhot, *et al. J. Virol.* 66:2670-2678, 1992).

Cytotoxicity assays are performed in the following manner. Target cells consist of either allogeneic HLA-matched or autologous EBV-transformed B lymphoblastoid cell line that are incubated overnight with the synthetic peptide epitope of the invention at 10 μM, and labeled with 100 μCi of ^{51}Cr (Amersham Corp., Arlington Heights, IL) for 1 hour after which they are washed four times with HBSS.

Cytolytic activity is determined in a standard 4 hour, split-well ^{51}Cr release assay using U-bottomed 96 well plates containing 3,000 targets/well. Stimulated PBMC are tested at effector/target (E/T) ratios of 20-50:1 on day 14. Percent cytotoxicity is determined from the formula: 100 x [(experimental release-spontaneous release)/maximum release-spontaneous release)]. Maximum release is determined by lysis of targets by detergent (2% Triton X-100; Sigma Chemical Co., St. Louis, MO). Spontaneous release is <25% of maximum release for all experiments.

The results of such an analysis indicate the extent to which HLA-restricted CTL populations have been stimulated by previous exposure to the TAA or TAA vaccine.

The class II restricted HTL responses may also be analyzed. Purified PBMC are cultured in a 96-well flat bottom plate at a density of $1.5x10^5$ cells/well and are stimulated with 10 μg/ml synthetic peptide, whole antigen, or PHA. Cells are routinely plated in replicates of 4-6 wells for each condition. After seven days of culture, the medium is removed and replaced with fresh medium containing 10U/ml IL-2. Two days later, 1 μCi ^{3}H-thymidine is added to each well and incubation is continued for an additional 18 hours. Cellular DNA is then harvested on glass fiber mats and analyzed for ^{3}H-thymidine incorporation. Antigen-specific T cell proliferation is calculated as the ratio of ^{3}H-thymidine incorporation in the presence of antigen divided by the ^{3}H-thymidine incorporation in the absence of antigen.

Example 18. Induction Of Specific CTL Response In Humans

A human clinical trial for an immunogenic composition comprising CTL and HTL epitopes of the invention is set up as an IND Phase I, dose escalation study. Such a trial is designed, for example, as follows:

A total of about 27 subjects are enrolled and divided into 3 groups:

Group I: 3 subjects are injected with placebo and 6 subjects are injected with 5 μg of peptide composition;

Group II: 3 subjects are injected with placebo and 6 subjects are injected with 50 μg peptide composition;

Group III: 3 subjects are injected with placebo and 6 subjects are injected with 500 μg of peptide composition.

After 4 weeks following the first injection, all subjects receive a booster inoculation at the same dosage. Additional booster inoculations can be administered on the same schedule.

The endpoints measured in this study relate to the safety and tolerability of the peptide composition as well as its immunogenicity. Cellular immune responses to the peptide composition are an index of the intrinsic activity of the peptide composition, and can therefore be viewed as a measure of biological efficacy. The following summarize the clinical and laboratory data that relate to safety and efficacy endpoints.

Safety: The incidence of adverse events is monitored in the placebo and drug treatment group and assessed in terms of degree and reversibility.

Evaluation of Vaccine Efficacy: For evaluation of vaccine efficacy, subjects are bled before and after injection. Peripheral blood mononuclear cells are isolated from fresh heparinized blood by Ficoll-Hypaque density gradient centrifugation, aliquoted in freezing media and stored frozen. Samples are assayed for CTL and HTL activity.

The vaccine is found to be both safe and efficacious.

Example 19. Therapeutic Use in Cancer Patients

Evaluation of vaccine compositions are performed to validate the efficacy of the CTL-HTL peptide compositions in cancer patients. The main objectives of the trials are to determine an effective dose and regimen for inducing CTLs in cancer patients, to establish the safety of inducing a CTL and HTL response in these patients, and to see to what extent activation of CTLs improves the clinical picture of cancer patients, as

manifested by a reduction in tumor cell numbers. Such a study is designed, for example, as follows:

The studies are performed in multiple centers. The trial design is an open-label, uncontrolled, dose escalation protocol wherein the peptide composition is administered as a single dose followed six weeks later by a single booster shot of the same dose. The dosages are 50, 500 and 5,000 micrograms per injection. Drug-associated adverse effects (severity and reversibility) are recorded.

There are three patient groupings. The first group is injected with 50 micrograms of the peptide composition and the second and third groups with 500 and 5,000 micrograms of peptide composition, respectively. The patients within each group range in age from 21-65, include both males and females (unless the tumor is sex-specific, *e.g.*, breast or prostate cancer), and represent diverse ethnic backgrounds.

Example 20. Induction of CTL Responses Using a Prime Boost Protocol

A prime boost protocol similar in its underlying principle to that used to evaluate the efficacy of a DNA vaccine in transgenic mice, which was described in Example 12, may also be used for the administration of the vaccine to humans. Such a vaccine regimen may include an initial administration of, for example, naked DNA followed by a boost using recombinant virus encoding the vaccine, or recombinant protein/polypeptide or a peptide mixture administered in an adjuvant.

For example, the initial immunization may be performed using an expression vector, such as that constructed in Example 11, in the form of naked nucleic acid administered IM (or SC or ID) in the amounts of 0.5-5 mg at multiple sites. The nucleic acid (0.1 to 1000 μg) can also be administered using a gene gun. Following an incubation period of 3-4 weeks, a booster dose is then administered. The booster can be recombinant fowlpox virus administered at a dose of 5-10^7 to 5x10^9 pfu. An alternative recombinant virus, such as an MVA, canarypox, adenovirus, or adeno-associated virus, can also be used for the booster, or the polyepitopic protein or a mixture of the peptides can be administered. For evaluation of vaccine efficacy, patient blood samples will be obtained before immunization as well as at intervals following administration of the initial vaccine and booster doses of the vaccine. Peripheral blood mononuclear cells are isolated from fresh heparinized blood by Ficoll-Hypaque density gradient centrifugation, aliquoted in freezing media and stored frozen. Samples are assayed for CTL and HTL activity.

Analysis of the results will indicate that a magnitude of response sufficient to achieve protective immunity against cancer is generated.

Example 21. Administration of Vaccine Compositions Using Dendritic Cells

Vaccines comprising peptide epitopes of the invention may be administered using dendritic cells. In this example, the immunogenic peptide epitopes are used to elicit a CTL and/or HTL response *ex vivo*.

Ex vivo CTL or HTL responses to a particular tumor-associated antigen are induced by incubating in tissue culture the patient's, or genetically compatible, CTL or HTL precursor cells together with a source of antigen-presenting cells (APC), such as dendritic cells, and the appropriate immunogenic peptides. After an appropriate incubation time (typically about 7-28 days), in which the precursor cells are activated and expanded into effector cells, the cells are infused back into the patient, where they will destroy (CTL) or facilitate destruction (HTL) of their specific target cells, *i.e.*, tumor cells.

Alternatively, the peptide-pulsed dendritic cells may be administered to the patient to stimulate a CTL response *in vivo*. In this method, dendritic cells are isolated as described in Example 3. The dendritic cell population is expanded and pulsed with a vaccine comprising peptide CTL and HTL epitopes of the invention. The dendritic cells are infused back into the patient to elicit CTL and HTL responses *in vivo*. The induced CTL and HTL then destroy (CTL) or facilitate destruction (HTL) of the specific target tumor cells that bear the proteins from which the epitopes in the vaccine are derived.

Example 22. Alternative Method of Identifying Motif-Bearing Peptides

Another way of identifying motif-bearing peptides is to elute them from cells bearing defined MHC molecules. For example, EBV transformed B cell lines used for tissue typing, have been extensively characterized to determine which HLA molecules they express. In certain cases these cells express only a single type of HLA molecule. These cells can then be infected with a pathogenic organism or transfected with nucleic acids that express the tumor antigen of interest. Thereafter, peptides produced by endogenous antigen processing of peptides produced consequent to infection (or as a result of transfection) will bind to HLA molecules within the cell and be transported and displayed on the cell surface.

The peptides are then eluted from the HLA molecules by exposure to mild acid conditions and their amino acid sequence determined, e.g., by mass spectral analysis (*e.g.*, Kubo *et al.*, *J. Immunol.* 152:3913, 1994). Because, as disclosed herein, the majority of peptides that bind a particular HLA molecule are motif-bearing, this is an alternative modality for obtaining the motif-bearing peptides correlated with the particular HLA molecule expressed on the cell.

Alternatively, cell lines that do not express any endogenous HLA molecules can be transfected with an expression construct encoding a single HLA allele. These cells may then be used as described, *i.e.*, they may be infected with a pathogenic organism or transfected with nucleic acid encoding an antigen of interest to isolate peptides corresponding to the pathogen or antigen of interest that have been presented on the cell surface. Peptides obtained from such an analysis will bear motif(s) that correspond to binding to the single HLA allele that is expressed in the cell.

As appreciated by one in the art, one can perform a similar analysis on a cell bearing more than one HLA allele and subsequently determine peptides specific for each HLA allele expressed. Moreover, one of skill would also recognize that means other than infection or transfection, such as loading with a protein antigen, can be used to provide a source of antigen to the cell.

The above examples are provided to illustrate the invention but not to limit its scope. For example, the human terminology for the Major Histocompatibility Complex, namely HLA, is used throughout this document. It is to be appreciated that these principles can be extended to other species as well. Thus, other variants of the invention will be readily apparent to one of ordinary skill in the art and are encompassed by the appended claims. All publications, patents, and patent application cited herein are hereby incorporated by reference for all purposes.

TABLE I

SUPERMOTIFS	POSITION 2 (Primary Anchor)	POSITION 3 (Primary Anchor)	POSITION C Terminus (Primary Anchor)
A1	**T***L VMS*		**FWY**
A2	**LIVM***ATQ*		**IV***MATL*
A3	**VSMA***TLI*		**RK**
A24	**YF***WIVLMT*		**FI***YWLM*
B7	**P**		**VILF***MWYA*
B27	**RHK**		**FYL***WMIVA*
B44	**E***D*		**FWYLIMVA**
B58	**ATS**		**FWY***LIVMA*
B62	**QL***IVMP*		**FWY***MIVLA*
MOTIFS			
A1	**TSM**		**Y**
A1		**DE***AS*	**Y**
A2.1	**LM***VQIAT*		**V***LIMAT*
A3	**LMVISATF***CGD*		**KYR***HFA*
A11	**VTMLISAGN***CDF*		**K***RYH*
A24	**YFW***M*		**FLIW**
A*3101	**MVT***ALIS*		**R***K*
A*3301	**MVALF***IST*		**RK**
A*6801	**AVT***MSLI*		**RK**
B*0702	**P**		**LMF***WYAIV*
B*3501	**P**		**LMFWY***IVA*
B51	**P**		**LIVF***WYAM*
B*5301	**P**		**IMFWY***ALV*
B*5401	**P**		**ATIV***LMFWY*

Bolded residues are preferred, italicized residues are less preferred: A peptide is considered motif-bearing if it has primary anchors at each primary anchor position for a motif or supermotif as specified in the above table.

TABLE Ia

SUPERMOTIFS	POSITION 2 (Primary Anchor)	POSITION 3 (Primary Anchor)	POSITION C Terminus (Primary Anchor)
A1	**TI***LVMS*		**FWY**
A2	*VQAT*		**V***LIMAT*
A3	**VSMA***TLI*		**RK**
A24	**YF***WIVLMT*		**FI***YWLM*
B7	**P**		**VILF***MWYA*
B27	**RHK**		**FYL***WMIVA*
B58	**ATS**		**FWY***LIVMA*
B62	**QL***IVMP*		**FWY***MIVLA*
MOTIFS			
A1	**TSM**		**Y**
A1		**DE***AS*	**Y**
A2.1	*VQAT**		**V***LIMAT*
A3.2	**LMVISATF***CGD*		**KYR***HFA*
A11	**VTMLISAGN***CDF*		**K***RHY*
A24	**YFW**		**FLIW**

*If 2 is V, or Q, the C-term is not L

Bolded residues are preferred, italicized residues are less preferred: A peptide is considered motif-bearing if it has primary anchors at each primary anchor position for a motif or supermotif as specified in the above table.

TABLE II

		POSITION								
		1	2	3	4	5	6	7	8	C-terminus
SUPERMOTIFS										
A1			1° Anchor T*LVMS*							1° Anchor FWY
A2			1° Anchor LIVM*ATQ*							1° Anchor LIVMAT
A3	preferred		1° Anchor VSMA*TLI*	YFW (4/5)			YFW (3/5)	YFW (4/5)	P (4/5)	1°Anchor RK
	deleterious	DE (3/5); P (5/5)		DE (4/5)						
A24			1° Anchor YF*WIVLM* *T*							1° Anchor FI*YWLM*
B7	preferred	FWY (5/5) LIVM (3/5)	1°Anchor P	FWY (4/5)					FWY (3/5)	1°Anchor VILF*MWYA*
	deleterious	DE (3/5); P(5/5); G(4/5); A(3/5); QN (3/5)				DE (3/5)	G (4/5)	QN (4/5)	DE (4/5)	
B27			1° Anchor RHK							1° Anchor FYL*WMIVA*
B44			1° Anchor E*D*							1° Anchor FWYLIMVA
B58			1° Anchor ATS							1° Anchor FWY*LIVMA*
B62			1° Anchor QL*IVMP*							1° Anchor FWY*MIVLA*

		POSITION							
		1	2	3	4	5	6	7	8	C-terminus

		POSITION							
		1	2	3	4	5	6	7	8	C-terminus
MOTIFS										
A1 9-mer	preferred	GFYW	1°Anchor STM	DEA	YFW		P	DEQN	YFW	1°Anchor Y
	deleterious	DE		RHKLIVM P	A	G	A			
A1 9-mer	preferred	GRHK	ASTCLIV M	1°Anchor DE*AS*	GSTC		ASTC	LIVM	DE	1°Anchor Y
	deleterious	A	RHKDEPY FW		DE	PQN	RHK	PG	GP	

		POSITION									
		1	2	3	4	5	6	7	8	9 or C-terminus	C-terminus
A1 10-mer	peferred	YFW	1°Anchor STM	DEAQN	A	YFWQN		PASTC	GDE	P	1°Anchor Y
	deleterious	GP		RHKGLIVM	DE	RHK	QNA	RHKYFW	RHK	A	
A1 10-mer	preferred	YFW	STCLIVM	1°Anchor DE*AS*	A	YFW		PG	G	YFW	1°Anchor Y
	deleterious	RHK	RHKDEPYFW			P	G		PRHK	QN	
A2.1 9-mer	preferred	YFW	1°Anchor LM*IVQAT*	YFW	STC	YFW		A	P	1°Anchor V*LIMAT*	
	deleterious	DEP		DERKH			RKH	DERKH			
A2.1 10-mer	preferred	AYFW	1°Anchor LM*IVQAT*	LVIM	G		G		FYWLVIM		1°Anchor V*LIMAT*
	deleterious	DEP		DE	RKHA	P		RKH	DERKH	RKH	

		POSITION									
		1	2	3	4	5	6	7	8	9 or C-terminus	C-terminus
A3	preferred	RHK	1°Anchor LMVISAT F*CGD*	YFW	PRHKYFW	A	YFW		P	1°Anchor KYR*HFA*	
	deleterious	DEP		DE							
A11	preferred	A	1°Anchor VTLMISA GN*CDF*	YFW	YFW	A	YFW	YFW	P	1°Anchor K*RYH*	
	deleterious	DEP						A	G		
A24 9-mer	preferred	YFWRHK	1°Anchor YFW*M*		STC			YFW	YFW	1°Anchor FLIW	
	deleterious	DEG		DE	G	QNP	DERHK	G	AQN		
A24 10-mer	preferred		1°Anchor YFW*M*		P	YFWP		P			1°Anchor FLIW
	deleterious			GDE	QN	RHK	DE	A	QN	DEA	

		POSITION									
		1	2	3	4	5	6	7	8	9 or C-terminus	C-terminus
A3101	preferred	RHK	1°Anchor MVT*ALIS*	YFW	P		YFW	YFW	AP	1°Anchor R*K*	
	deleterious	DEP		DE		ADE	DE	DE	DE		
A3301	preferred		1°Anchor MVALF*IS T*	YFW				AYFW		1°Anchor RK	
	deleterious	GP		DE							
A6801	preferred	YFWSTC	1°Anchor AVT*MSLI*			YFWLIV M		YFW	P	1°Anchor RK	
	deleterious	GP		DEG		RHK			A		
B0702	preferred	RHKFWY	1°Anchor P	RHK		RHK	RHK	RHK	PA	1°Anchor LMF*WYAIV*	
	deleterious	DEQNP		DEP	DE	DE	GDE	QN	DE		
B3501	preferred	FWYLIVM	1°Anchor P	FWY				FWY		1°Anchor LMFWY*IVA*	
	deleterious	AGP				G	G				

		POSITION									
		1	2	3	4	5	6	7	8	9 or C-terminus	C-terminus
B51	preferred	LIVMFWY	1°Anchor P	FWY	STC	FWY		G	FWY	1°Anchor LIVF*WYAM*	
	deleterious	AGPDERHKSTC				DE	G	DEQN	GDE		
B5301	preferred	LIVMFWY	1°Anchor P	FWY	STC	FWY		LIVMFWY	FWY	1°Anchor IMFWY*ALV*	
	deleterious	AGPQN					G	RHKQN	DE		
B5401	preferred	FWY	1°Anchor P	FWYLIVM		LIVM		ALIVM	FWYAP	1°Anchor ATIV*LMFW Y*	
	deleterious	GPQNDE		GDESTC		RHKDE	DE	QNDGE	DE		

Italicized residues indicate less preferred or "tolerated" residues.
The information in Table II is specific for 9-mers unless otherwise specified.

TABLE III

		POSITION								
MOTIFS		1° anchor 1	2	3	4	5	1° anchor 6	7	8	9
DR4	preferred	FMY*LIVW*	M	T		I	VST*CPALIM*	MH		MH
	deleterious				W			R		WDE
DR1	preferred	MF*LIVWY*			PAMQ		VMAT*SPLIC*	M		AVM
	deleterious		C	CH	FD	CWD		GDE	D	
DR7	preferred	MF*LIVWY*	M	W	A		IVMSA*CTPL*	M		IV
	deleterious		C		G			GRD	N	G
DR Supermotif		MF*LIVWY*					VMSTA*CPLI*			

DR3 MOTIFS	1° anchor 1	2	3	1° anchor 4	5	1° anchor 6
motif a preferred	LIVMFY			D		
motif b preferred	LIVMFAY			DNQEST		KRH

Italicized residues indicate less preferred or "tolerated" residues.

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Table IV. HLA Class I Standard Peptide Binding Affinity.

ALLELE	STANDARD PEPTIDE	SEQUENCE	STANDARD BINDING AFFINITY (nM)
A*0101	944.02	YLEPAIAKY	25
A*0201	941.01	FLPSDYFPSV	5.0
A*0202	941.01	FLPSDYFPSV	4.3
A*0203	941.01	FLPSDYFPSV	10
A*0205	941.01	FLPSDYFPSV	4.3
A*0206	941.01	FLPSDYFPSV	3.7
A*0207	941.01	FLPSDYFPSV	23
A*6802	1072.34	YVIKVSARV	8.0
A*0301	941.12	KVFPYALINK	11
A*1101	940.06	AVDLYHFLK	6.0
A*3101	941.12	KVFPYALINK	18
A*3301	1083.02	STLPETYVVRR	29
A*6801	941.12	KVFPYALINK	8.0
A*2402	979.02	AYIDNYNKF	12
B*0702	1075.23	APRTLVYLL	5.5
B*3501	1021.05	FPFKYAAAF	7.2
B51	1021.05	FPFKYAAAF	5.5
B*5301	1021.05	FPFKYAAAF	9.3
B*5401	1021.05	FPFKYAAAF	10

Table V. HLA Class II Standard Peptide Binding Affinity.

Allele	Nomenclature	Standard Peptide	Sequence	Binding Affinity (nM)
DRB1*0101	DR1	515.01	PKYVKQNTLKLAT	5.0
DRB1*0301	DR3	829.02	YKTIAFDEEARR	300
DRB1*0401	DR4w4	515.01	PKYVKQNTLKLAT	45
DRB1*0404	DR4w14	717.01	YARFQSQTTLKQKT	50
DRB1*0405	DR4w15	717.01	YARFQSQTTLKQKT	38
DRB1*0701	DR7	553.01	QYIKANSKFIGITE	25
DRB1*0802	DR8w2	553.01	QYIKANSKFIGITE	49
DRB1*0803	DR8w3	553.01	QYIKANSKFIGITE	1600
DRB1*0901	DR9	553.01	QYIKANSKFIGITE	75
DRB1*1101	DR5w11	553.01	QYIKANSKFIGITE	20
DRB1*1201	DR5w12	1200.05	EALIHQLKINPYVLS	298
DRB1*1302	DR6w19	650.22	QYIKANAKFIGITE	3.5
DRB1*1501	DR2w2β1	507.02	GRTQDENPVVHFFKNIV TPRTPPP	9.1
DRB3*0101	DR52a	511	NGQIGNDPNRDIL	470
DRB4*0101	DRw53	717.01	YARFQSQTTLKQKT	58
DRB5*0101	DR2w2β2	553.01	QYIKANSKFIGITE	20

The "Nomenclature" column lists the allelic designations used in Tables XIX and XX.

Table VI

HLA-supertype	Allelle-specific HLA-supertype members	
	Verified[a]	Predicted[b]
A1	A*0101, A*2501, A*2601, A*2602, A*3201	A*0102, A*2604, A*3601, A*4301, A*8001
A2	A*0201, A*0202, A*0203, A*0204, A*0205, A*0206, A*0207, A*0209, A*0214, A*6802, A*6901	A*0208, A*0210, A*0211, A*0212, A*0213
A3	A*0301, A*1101, A*3101, A*3301, A*6801	A*0302, A*1102, A*2603, A*3302, A*3303, A*3401, A*3402, A*6601, A*6602, A*7401
A24	A*2301, A*2402, A*3001	A*2403, A*2404, A*3002, A*3003
B7	B*0702, B*0703, B*0704, B*0705, B*1508, B*3501, B*3502, B*3503, B*3503, B*3504, B*3505, B*3506, B*3507, B*3508, B*5101, B*5102, B*5103, B*5104, B*5105, B*5301, B*5401, B*5501, B*5502, B*5601, B*5602, B*6701, B*7801	B*1511, B*4201, B*5901
B27	B*1401, B*1402, B*1509, B*2702, B*2703, B*2704, B*2705, B*2706, B*3801, B*3901, B*3902, B*7301	B*2701, B*2707, B*2708, B*3802, B*3903, B*3904, B*3905, B*4801, B*4802, B*1510, B*1518, B*1503
B44	B*1801, B*1802, B*3701, B*4402, B*4403, B*4404, B*4001, B*4002, B*4006	B*4101, B*4501, B*4701, B*4901, B*5001
B58	B*5701, B*5702, B*5801, B*5802, B*1516, B*1517	
B62	B*1501, B*1502, B*1513, B*5201	B*1301, B*1302, B*1504, B*1505, B*1506, B*1507, B*1515, B*1520, B*1521, B*1512, B*1514, B*1510

a. Verified alleles inclueds alleles whose specificity has been determined by pool sequencing analysis, peptide binding assays, or by analysis of the sequences of CTL epitopes.

b. Predicted alleles are alleles whose specificity is predicted on the basis of B and F pocket structure to overlap with the supertype specificity.

Table VII
HER2/NEU A01 Supermotif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*0101	SEQ ID NO.
PTNASLSF	66	8		1
VTYNTDTF	272	8		2
GTVYKGIW	732	8		3
FTHQSDVW	899	8		4
VTACPYNY	296	8	0.1000	5
MTFGAKPY	916	8	-0.0021	6
PTAENPEY	1241	8	0.0030	7
TILWKDIF	166	8		8
KIFGSLAF	369	8		9
DIQEVQGY	76	8		10
RILHNGAY	434	8		11
QIAKGMSY	828	8	-0.0021	12
PICTIDVY	945	8		13
SLPDLSVF	418	8		14
YLVPQQGF	1023	8		15
ELAALCRW	2	8		16
DLSYMPIW	607	8		17
TLEEITGY	402	8	-0.0021	18
DLVDAEEY	1016	8		19
IVRGTQLF	101	8		20
TVPWDQLF	479	8		21
VVVLGVVF	664	8		22
KVLGSGAF	724	8		23
TVWELMTF	911	8		24
LVPQQGFF	1024	8		25
VVKDVFAF	1180	8		26
GVKPDLSY	603	8		27
LVTQLMPY	796	8		28
YMIMVKCW	952	8		29
TSANIQEF	357	8		30
ESILRRRF	892	8		31
DSECRPRF	962	8		32
ASPLDSTF	997	8		33
GSQDLLNW	818	8		34
WSYGVTVW	906	8		35
DTILWKDIF	165	9		36
VTSANIQEF	356	9		37
HTVPWDQLF	478	9		38
VTVWELMTF	910	9		39
GTQLFEDNY	104	9	0.1800	40
ETLEEITGY	401	9	0.0430	41
LTCSPQPEY	1131	9	0.1300	42
RIVRGTQLF	100	9		43
SLAFLPESF	373	9		44
YLVPQQGFF	1023	9		45
TLQGLGISW	444	9		46
QLCARGHCW	513	9		47
HLDMLRHLY	42	9	9.1000	48
VLQGLPREY	546	9	0.0050	49
QLVTQLMPY	795	9	0.0024	50

Table VII
HER2/NEU A01 Supermotif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*0101	SEQ ID NO.
LLDIDETEY	869	9	7.6000	51
PLPSETDGY	1119	9	0.0017	52
LVTYNTDTF	271	9		53
LVVVLGVVF	663	9		54
GVVKDVFAF	1179	9		55
CVTACPYNY	295	9	0.0042	56
RMARDPQRF	978	9		57
PMCKGSRCW	197	9		58
SMPNPLGRY	281	9	0.0028	59
VMAGVGSPY	773	9	0 0400	60
LMTFGAKPY	915	9	0.0011	61
DSLPDLSVF	417	9		62
LSYMPIWKF	608	9		63
ASCVTACPY	293	9	0.0550	64
GSGAFGTVY	727	9	0.0011	65
ASPLDSTFY	997	9	0.0290	66
FSPAFDNLY	1213	9	0.0430	67
PTQCVNCSQF	525	10		68
ITGYLYISAW	406	10		69
LTLQGLGISW	443	10		70
FTHQSDVWSY	899	10	2.7000	71
GTPTAENPEY	1239	10	0.0630	72
LIHHNTHLCF	467	10		73
MIDSECRPRF	960	10		74
LIQRNPQLCY	154	10	0.0300	75
YLPTNASLSF	64	10		76
ALVTYNTDTF	270	10		77
PLQPEQLQVF	391	10		78
DLSYMPIWKF	607	10		79
LLVVVLGVVF	662	10		80
ALESILRRRF	890	10		81
QLCYQDTILW	160	10		82
HLCFVHTVPW	473	10		83
RLGSQDLLNW	816	10		84
ELHCPALVTY	265	10	0.0015	85
TLEEITGYLY	402	10	1.1000	86
RLLDIDETEY	868	10	1.3000	87
ELMTFGAKPY	914	10	0.0082	88
PLTCSPQPEY	1130	10	0 0072	89
AVTSANIQEF	355	10		90
KVKVLGSGAF	722	10		91
GVTVWELMTF	909	10		92
DVWSYGVTVW	904	10		93
DVYMIMVKCW	950	10		94
VVQGNLELTY	55	10	0.0180	95
RVLQGLPREY	545	10	0.0015	96
YVMAGVGSPY	772	10	1 1000	97
CMQIAKGMSY	826	10	0 3000	98
HSDCLACLHF	249	10		99
GSLAFLPESF	372	10		100

Table VII
HER2/NEU A01 Supermotif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*0101	SEQ ID NO.
PSEGAGSDVF	1077	10		101
ESMPNPEGRY	280	10	0.1800	102
CSKPCARVCY	334	10	0.0016	103
PSGVKPDLSY	601	10	0.0010	104
FSPAFDNLYY	1213	10	5.5000	105
ETHLDMLRHLY	40	11	0.2800	106
ETLEEITGYLY	401	11	0.4400	107
PTHDPSPLQRY	1102	11	0.0160	108
EITGYLYISAW	405	11		109
RLRIVRGTQLF	98	11		110
ALIHHNTHLCF	466	11		111
ILLVVVLGVVF	661	11		112
SLTLQGLGISW	442	11		113
FLQDIQEVQGY	73	11		114
VLIQRNPQLCY	153	11		115
VLGSGAFGTVY	725	11		116
FVHTVPWDQLF	476	11		117
QVVQGNLELTY	54	11		118
TVQLVTQLMPY	793	11		119
TVPLPSETDGY	1117	11		120
SMPNPEGRYTF	281	11		121
WMIDSECRPRF	959	11		122
DMGDLVDAEEY	1013	11	0 0027	123
KSPNHVKITDF	854	11		124
FSRMARDPQRF	976	11		125
CSPMCKGSRCW	195	11		126
FSPAFDNLYYW	1213	11		127
ASCVTACPYNY	293	11	0.1900	128

Table VIII

HER2/NEU A02 Supermotif with Binding Data

Sequence	Position	No. of Amino Acids	A*0201	A*0202	A*0203	A*0206	A*6802	SEQ ID NO.
AAKGLQSL	1094	8						129
AAKGLQSLPT	1094	10						130
AALCRWGL	4	8						131
AALCRWGLL	4	9						132
AALCRWGLLL	4	10	0.0010					133
AALCRWGLLLA	4	11						134
AAPQPHPPPA	1203	10						135
AARPAGAT	1159	8						136
AARPAGATL	1159	9	0 0001					137
AASTQVCT	20	8						138
AASTQVCTGT	20	10						139
AIKVLRENT	751	9						140
ALAVLDNGDPL	113	11						141
ALCRWGLL	5	8						142
ALCRWGLLL	5	9	0 0310					143
ALCRWGLLLA	5	10	0.0360	0.0022	0.8600	0.0019	0.0160	144
ALCRWGLLLAL	5	11						145
ALESILRRRFT	890	11						146
ALIHHNTHL	466	9	0 0210					147
ALLPPGAA	14	8						148
ALLPPGAAST	14	10	0.0001					149
ALVTYNTDT	270	9	0.0001					150
AMPNQAQM	705	8						151
AMPNQAQMRI	705	10	0.0007					152
AMPNQAQMRIL	705	11						153
AQMRILKET	710	9						154
AQMRILKETEL	710	11						155
ATLERPKT	1165	8						156
ATLERPKTL	1165	9						157
AVENPEYL	1190	8						158
AVENPEYLT	1190	9						159
AVLDNGDPL	115	9	0.0004					160
AVTSANIQEFA	355	11						161
AVVGILLV	657	8						162
AVVGILLVV	657	9	0 0007					163
AVVGILLVVV	657	10	0.0002					164
AVVGILLVVVL	657	11						165
CAIIYKDPPFCV	587	11						166
CARCKGPL	224	8						167
CARCKGPLPT	224	10						168
CARVCYGL	338	8						169
CARVCYGLGM	338	10	0.0011					170
CLHFNHSGI	255	9						171
CLTSTVQL	789	8						172
CLTSTVQLV	789	9	0.0340					173
CLTSTVQLVT	789	10						174
CMQIAKGM	826	8						175
CMQIAKGMSYL	826	11						176
CQPCPINCT	623	9						177
CQPQNGSV	567	8						178

Table VIII

HER2/NEU A02 Supermotif with Binding Data

Sequence	Position	No. of Amino Acids	A*0201	A*0202	A*0203	A*0206	A*6802	SEQ ID NO.
CQPQNGSVT	567	9						179
CQSLTRTV	212	8						180
CQSLTRTVCA	212	10						181
CQVVQGNL	53	8						182
CQVVQGNLEL	53	10						183
CQVVQGNLELT	53	11						184
CTGPKHSDCL	244	10						185
CTGPKHSDCLA	244	11						186
CTGTDMKL	26	8						187
CTGTDMKLRL	26	10						188
CTHSCVDL	630	8						189
CTIDVYMI	947	8						190
CTIDVYMIM	947	9						191
CTIDVYMIMV	947	10						192
CVARCPSGV	596	9	0.0004					193
CVDLDDKGCPA	634	11						194
CVEECRVL	540	8						195
CVEECRVLQGL	540	11						196
CVGEGLACHQL	504	11						197
CVNCSQFL	528	8						198
CVTACPYNYL	295	10	0.0001					199
DIDETEYHA	871	9						200
DIFHKNNQL	171	9	0.0002					201
DIFHKNNQLA	171	10						202
DIFHKNNQLAL	171	11						203
DIQEVQGYV	76	9	0.0001					204
DIQEVQGYVL	76	10	0.0001					205
DIQEVQGYVLI	76	11						206
DLAARNVL	845	8						207
DLAARNVLV	845	9	0.0002					208
DLDDKGCPA	636	9						209
DLGMGAAKGL	1089	10	0.0001					210
DLGPASPL	993	8						211
DLGPASPLDST	993	11						212
DLLEKGERL	933	9	0.0002					213
DLLNWCMQI	821	9	0.0002					214
DLLNWCMQIA	821	10						215
DLSVFQNL	421	8						216
DLSVFQNLQV	421	10	0.0003					217
DLSVFQNLQVI	421	11						218
DLVDAEEYL	1016	9	0.0002					219
DLVDAEEYLV	1016	10	0.0002					220
DMGDLVDA	1013	8						221
DMKLRLPA	30	8						222
DQDPPERGA	1224	9						223
DQLFRNPHQA	483	10						224
DQLFRNPHQAL	483	11						225
DTILWKDI	165	8						226
DVFAFGGA	1183	8						227
DVFAFGGAV	1183	9	0.0002					228

Table VIII
HER2/NEU A02 Supermotif with Binding Data

Sequence	Position	No. of Amino Acids	A*0201	A*0202	A*0203	A*0206	A*6802	SEQ ID NO.
DVFDGDLGM	1084	9						229
DVFDGDLGMGA	1084	11						230
DVGSCTLV	307	8						231
DVGSCTLVCPL	307	11						232
DVRLVHRDL	838	9	0 0002					233
DVRLVHRDLA	838	10						234
DVRLVHRDLAA	838	11						235
DVWSYGVT	904	8						236
DVWSYGVTV	904	9	0 0002					237
DVYMIMVKCWM	950	11						238
EADQCVACA	580	9						239
EAPRSPLA	1069	8						240
EAYVMAGV	770	8						241
EILDEAYV	766	8						242
EILDEAYVM	766	9						243
EILDEAYVMA	766	10						244
EILKGGVL	147	8						245
EILKGGVLI	147	9	0.0001					246
EITGYLYI	405	8						247
EITGYLYISA	405	10						248
ELAALCRWGL	2	10	0.0001					249
ELAALCRWGLL	2	11						250
ELGSGLAL	460	8						251
ELGSGLALI	460	9	0 0004					252
ELHCPALV	265	8						253
ELHCPALVT	265	9						254
ELQLRSLT	139	8						255
ELQLRSLTEI	139	10						256
ELQLRSLTEIL	139	11						257
ELRKVKVL	719	8						258
ELTYLPTNA	61	9						259
ELTYLPTNASL	61	11						260
ELVEPLTPSGA	695	11						261
ELVSEFSRM	971	9	0 0001					262
ELVSEFSRMA	971	10	0.0001					263
EQCAAGCT	238	8						264
EQLQVFET	395	8						265
EQLQVFETL	395	9						266
EQRASPLT	645	8						267
EQRASPLTSI	645	10						268
EQRASPLTSII	645	11						269
ETDGYVAPL	1123	9						270
ETDGYVAPLT	1123	10						271
ETELRKVKV	717	9						272
ETELRKVKVL	717	10						273
ETELVEPL	693	8						274
ETELVEPLT	693	9						275
ETEYHADGGKV	874	11						276
ETHLDMLRHL	40	10						277
ETLEEITGYL	401	10						278

Table VIII

HER2/NEU A02 Supermotif with Binding Data

Sequence	Position	No. of Amino Acids	A*0201	A*0202	A*0203	A*0206	A*6802	SEQ ID NO.
EVQGYVLI	79	8						279
EVQGYVLIA	79	9						280
EVRAVTSA	352	8						281
EVRAVTSANI	352	10						282
EVTAEDGT	321	8						283
FAGCKKIFGSL	364	11						284
FLPESFDGDPA	376	11						285
FLQDIQEV	73	8						286
FLRGQECV	534	8						287
FQNLQVIRGRI	425	11						288
FVHTVPWDQL	476	10	0.0001					289
FVVIQNEDL	986	9	0.0002					290
GAAKGLQSL	1093	9	0.0001					291
GAAKGLQSLPT	1093	11						292
GAAPQPHPPPA	1202	11						293
GAASTQVCT	19	9						294
GAASTQVCTGT	19	11						295
GACQPCPI	621	8						296
GACQPCPINCT	621	11						297
GAFGTVYKGI	729	10	0.0001					298
GAGSDVFDGDL	1080	11						299
GAKPYDGI	919	8						300
GAKPYDGIPA	919	10						301
GAMPNQAQM	704	9	0.0002					302
GAMPNQAQMRI	704	11						303
GAPPSTFKGT	1231	10						304
GASPGGLREL	131	10	0.0001					305
GATLERPKT	1164	9						306
GATLERPKTL	1164	10	0.0002					307
GAVENPEYL	1189	9	0.0002					308
GAVENPEYLT	1189	10						309
GAYSLTLQGL	439	10	0.0030					310
GICELHCPA	262	9						311
GICELHCPAL	262	10	0.0005					312
GICELHCPALV	262	11						313
GICLTSTV	787	8						314
GICLTSTVQL	787	10	0.0004					315
GICLTSTVQLV	787	11						316
GILIKRRQQKI	672	11						317
GILLVVVL	660	8						318
GILLVVVLGV	660	10	0.0007					319
GILLVVVLGVV	660	11						320
GIPAREIPDL	925	10	0.0001					321
GIPAREIPDLL	925	11						322
GISWLGLRSL	449	10	0.0003					323
GIWIPDGENV	737	10	0.0002					324
GLACHQLCA	508	9	0.0120	0.0001	0.0790	0.0001	0.0044	325
GLALHHNT	464	9						326
GLALHHNTHL	464	11						327
GLARLLDI	865	8						328

TableVIII
HER2/NEU A02 Supermotif with Binding Data

Sequence	Position	No. of Amino Acids	A*0201	A*0202	A*0203	A*0206	A*6802	SEQ ID NO.
GLARLLDIDET	865	11						329
GLEPSEEEA	1062	9						330
GLGISWLGL	447	9	0 0018					331
GLGMEHLREV	344	10	0.0017					332
GLLLALLPPGA	10	11						333
GLPREYVNA	549	9						334
GLRELQLRSL	136	10	0.0001					335
GLRELQLRSLT	136	11						336
GLRSLREL	454	8						337
GMEHLREV	346	8						338
GMEHLREVRA	346	10						339
GMEHLREVRAV	346	11						340
GMGAAKGL	1091	8						341
GMGAAKGLQSL	1091	11						342
GMSYLEDV	832	8						343
GMSYLEDVRL	832	10	0.0017					344
GMSYLEDVRLV	832	11						345
GQECVEECRV	537	10						346
GQECVEECRVL	537	11						347
GTDMKLRL	28	8						348
GTDMKLRLPA	28	10						349
GTPTAENPEYL	1239	11						350
GTQLFEDNYA	104	10						351
GTQLFEDNYAL	104	11						352
GTVYKGIWI	732	9						353
GVGSPYVSRL	776	10	0 0001					354
GVGSPYVSRLL	776	11						355
GVKPDLSYM	603	9						356
GVKPDLSYMPI	603	11						357
GVLIQRNPQL	152	10	0.0036					358
GVTVWELM	909	8						359
GVTVWELMT	909	9						360
GVVFGILI	668	8						361
GVVKDVFA	1179	8						362
HADGGKVPI	878	9	0 0002					363
HLCFVHTV	473	8						364
HLDMLRHL	42	8						365
HLREVRAV	349	8						366
HLREVRAVT	349	9						367
HLREVRAVTSA	349	11						368
HLYQGCQV	48	8						369
HLYQGCQVV	48	9	0.0340					370
HQALLHTA	490	8						371
HQSDVWSYGV	901	10						372
HQSDVWSYGVT	901	11						373
HTANRPEDECV	495	11						374
HTVPWDQL	478	8						375
HVKITDFGL	858	9	0.0002					376
HVKITDFGLA	858	10						377
HVRENRGRL	809	9	0 0002					378

TableVIII

HER2/NEU A02 Supermotif with Binding Data

Sequence	Position	No. of Amino Acids	A*0201	A*0202	A*0203	A*0206	A*6802	SEQ ID NO.
IAHNQVRQV	86	9						379
IAHNQVRQVPL	86	11						380
IAKGMSYL	829	8						381
IAKGMSYLEDV	829	11						382
IISAVVGI	654	8						383
IISAVVGIL	654	9	0 0005					384
IISAVVGILL	654	10	0 0120					385
IISAVVGILLV	654	11						386
ILDEAYVM	767	8						387
ILDEAYVMA	767	9	0.0210	0 0001	0 0024	0.0012	0.0003	388
ILDEAYVMAGV	767	11						389
ILHNGAYSL	435	9	0.2100					390
ILHNGAYSLT	435	10						391
ILHNGAYSLTL	435	11						392
ILIKRRQQKI	673	10						393
ILKETELRKV	714	10	0 0001					394
ILKGGVLI	148	8						395
ILLVVVLGV	661	9	0 0020					396
ILLVVVLGVV	661	10	0 0006					397
IMVKCWMI	954	8						398
IQEFAGCKKI	361	10						399
IQEVQGYV	77	8						400
IQEVQGYVL	77	9						401
IQEVQGYVLI	77	10						402
IQEVQGYVLIA	77	11						403
IQNEDLGPA	989	9						404
ITDFGLARL	861	9						405
ITDFGLARLL	861	10						406
ITGYLYISA	406	9						407
KANKEILDEA	762	10						408
KIFGSLAFL	369	9	0.1500					409
KIPVAIKV	747	8						410
KIPVAIKVL	747	9	0.0002					411
KIRKYTMRRL	681	10	0 0001					412
KIRKYTMRRLL	681	11						413
KITDFGLA	860	8						414
KITDFGLARL	860	10	0.0020					415
KITDFGLARLL	860	11						416
KLRLPASPET	32	10						417
KTLSPGKNGV	1171	10						418
KTLSPGKNGVV	1171	11						419
KVKVLGSGA	722	9						420
KVLGSGAFGT	724	10						421
KVLGSGAFGTV	724	11						422
KVLRENTSPKA	753	11						423
KVPIKWMA	883	8						424
KVPIKWMAL	883	9	0 0002					425
LAALCRWGL	3	9						426
LAALCRWGLL	3	10	0.0022					427
LAALCRWGLLL	3	11						428

Table VIII

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Sequence	Position	No. of Amino Acids	A*0201	A*0202	A*0203	A*0206	A*6802	SEQ ID NO.
LAARNVLV	846	8						429
LACHQLCA	509	8						430
LACLHFNHSGI	253	11						431
LALIHHNT	465	8						432
LALIHHNTHL	465	10						433
LALLPPGA	13	8						434
LALLPPGAA	13	9						435
LALLPPGAAST	13	11						436
LALTLIDT	179	8						437
LAPSEGAGSDV	1075	11						438
LARLLDIDET	866	10						439
LAVLDNGDPL	114	10	0.0002					440
LIAHNQVRQV	85	10	0.0001					441
LIDTNRSRA	183	9						442
LIHHHNTHL	467	8						443
LIHHHNTHLCFV	467	11						444
LIKRRQQKI	674	9						445
LIQRNPQL	154	8						446
LLALLPPGA	12	9	0.0008					447
LLALLPPGAA	12	10	0.0006					448
LLDIDETEYHA	869	11						449
LLEDDDMGDL	1008	10	0.0001					450
LLEDDDMGDLV	1008	11						451
LLEKGERL	934	8						452
LLGICLTST	785	9						453
LLGICLTSTV	785	10	0.0490					454
LLLALLPPGA	11	10	0.0054					455
LLLALLPPGAA	11	11						456
LLNWCMQI	822	8						457
LLNWCMQIA	822	9	0.0046					458
LLPPGAAST	15	9	0.0007					459
LLPPGAASTQV	15	11						460
LLQETELV	690	8						461
LLQETELVEPL	690	11						462
LLVVVLGV	662	8						463
LLVVVLGVV	662	9	0.0001					464
LMPYGCLL	800	8						465
LMPYGCLLDHV	800	11						466
LQDIQEVQGYV	74	11						467
LQETELVEPL	691	10						468
LQETELVEPLT	691	11						469
LQGLGISWL	445	9						470
LQGLGISWLGL	445	11						471
LQGLPREYV	547	9						472
LQGLPREYVNA	547	11						473
LQLRSLTEI	140	9						474
LQLRSLTEIL	140	10						475
LQPEQLQV	392	8						476
LQPEQLQVFET	392	11						477
LQRLRIVRGT	96	10						478

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Sequence	Position	No. of Amino Acids	A*0201	A*0202	A*0203	A*0206	A*6802	SEQ ID NO.
LQRYSEDPT	1109	9						479
LQRYSEDPTV	1109	10						480
LQVFETLEEI	397	10						481
LQVFETLEEIT	397	11						482
LQVIRGRI	428	8						483
LQVIRGRIL	428	9						484
LTCSPQPEYV	1131	10						485
LTEILKGGV	145	9						486
LTEILKGGVL	145	10						487
LTEILKGGVLI	145	11						488
LTLIDTNRSRA	181	11						489
LTLQGLGI	443	8						490
LTLQGLGISWL	443	11						491
LTPQGGAA	1197	8						492
LTPSGAMPNQA	700	11						493
LTRTVCAGGCA	215	11						494
LTSIISAV	651	8						495
LTSIISAVV	651	9						496
LTSIISAVVGI	651	11						497
LTSTVQLV	790	8						498
LTSTVQLVT	790	9						499
LTSTVQLVTQL	790	11						500
LTYLPTNA	62	8						501
LTYLPTNASL	62	10						502
LVCPLIINQEV	313	10	0.0002					503
LVCPLIINQEVT	313	11						504
LVDAEEYL	1017	8						505
LVDAEEYLV	1017	9	0.0030					506
LVEPLTPSGA	696	10						507
LVEPLTPSGAM	696	11						508
LVHRDLAA	841	8						509
LVHRDLAARNV	841	11						510
LVKSPNHV	852	8						511
LVKSPNHVKI	852	10						512
LVKSPNHVKIT	852	11						513
LVSEFSRM	972	8	0.0001					514
LVSEFSRMA	972	9	0.0001					515
LVTQLMPYGCL	796	11						516
LVTYNTDT	271	8						517
LVVVLGVV	663	8						518
LVVVLGVVFGI	663	11						519
MAGVGSPYV	774	9	0.0014					520
MARDPQRFV	979	9	0.0001					521
MARDPQRFVV	979	10						522
MARDPQRFVVI	979	11						523
MIMVKCWM	953	8						524
MIMVKCWMI	953	9	0.0051					525
MLRHLYQGCQV	45	11						526
MQIAKGMSYL	827	10						527
MTFGAKPYDGI	916	11						528

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Sequence	Position	No. of Amino Acids	A*0201	A*0202	A*0203	A*0206	A*6802	SEQ ID NO.
MVHHRHRSSST	1042	11						529
NASLSFLQDI	68	10	0.0001					530
NIQEFAGCKKI	360	11						531
NLELTYLPT	59	9						532
NLELTYLPTNA	59	11						533
NLQVIRGRI	427	9						534
NLQVIRGRIL	427	10	0.0001					535
NQAQMRIL	708	8						536
NQAQMRILKET	708	11						537
NQEVTAEDGT	319	10						538
NQLALTLI	177	8						539
NQLALTLIDT	177	10						540
NQVRQVPL	89	8						541
NQVRQVPLQRL	89	11						542
NTAPLQPEQL	388	10						543
NTDTFESM	275	8						544
NTHLCFVHT	471	9						545
NTHLCFVHTV	471	10						546
NTSPKANKEI	758	10						547
NTSPKANKEIL	758	11						548
NTTPVTGA	125	8						549
NVKIPVAI	745	8						550
NVKIPVAIKV	745	10	0.0001					551
NVKIPVAIKVL	745	11						552
NVLVKSPNHV	850	10	0.0001					553
PAARPAGA	1158	8						554
PAARPAGAT	1158	9						555
PAARPAGATL	1158	10	0.0001					556
PAEQRASPL	643	9	0.0001					557
PAEQRASPLT	643	10						558
PAFSPAFDNL	1211	10	0.0001					559
PAGATLERPKT	1162	11						560
PALVTYNT	269	8						561
PALVTYNTDT	269	10						562
PAPGAGGM	1035	8						563
PAPGAGGMV	1035	9						564
PAREIPDL	927	8						565
PAREIPDLL	927	9	0.0001					566
PASNTAPL	385	8						567
PASPETHL	36	8						568
PASPETHLDM	36	10	0.0001					569
PASPETHLDML	36	11						570
PASPLDST	996	8						571
PICTIDVYM	945	9						572
PICTIDVYMI	945	10						573
PICTIDVYMIM	945	11						574
PIKWMALESI	885	10						575
PIKWMALESIL	885	11						576
PINCTHSCV	627	9	0.0002					577
PINCTHSCVDL	627	11						578

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Sequence	Position	No. of Amino Acids	A*0201	A*0202	A*0203	A*0206	A*6802	SEQ ID NO.
PIWKFPDEEGA	612	11						579
PLAPSEGA	1074	8						580
PLDSTFYRSL	999	10	0.0001					581
PLDSTFYRSLL	999	11						582
PLHNQEVT	316	8						583
PLHNQEVTA	316	9						584
PLNNTTPV	122	8						585
PLNNTTPVT	122	9						586
PLNNTTPVTGA	122	11						587
PLPAARPA	1156	8						588
PLPAARPAGA	1156	10						589
PLPAARPAGAT	1156	11						590
PLPSETDGYV	1119	10	0.0001					591
PLPSETDGYVA	1119	11						592
PLQPEQLQV	391	9	0.0002					593
PLQRLRIV	95	8						594
PLQRLRIVRGT	95	11						595
PLQRYSEDPT	1108	10						596
PLQRYSEDPTV	1108	11						597
PLTCSPQPEYV	1130	11						598
PLTPSGAM	699	8						599
PLTSHSA	650	8						600
PLTSHSAV	650	9	0.0015					601
PLTSHSAVV	650	10	0.0003					602
PQLCYQDT	159	8						603
PQLCYQDTI	159	9						604
PQLCYQDTIL	159	10						605
PQPEYVNQPDV	1135	11						606
PQPHPPPA	1205	8						607
PQPPICTI	942	8						608
PQPPICTIDV	942	10						609
PQPPSPREGPL	1147	11						610
PQQGFFCPDPA	1026	11						611
PTAENPEYL	1241	9						612
PTAENPEYLGL	1241	11						613
PTDCCHEQCA	232	10						614
PTDCCHEQCAA	232	11						615
PTHDPSPL	1102	8						616
PTNASLSFL	66	9						617
PTQCVNCSQFL	525	11						618
PTVPLPSET	1116	9						619
PVAIKVLRENT	749	11						620
PVTGASPGGL	128	10	0.0001					621
QAQMRILKET	709	10						622
QIAKGMSYL	828	9	0.0006					623
QLALTLIDT	178	9						624
QLCYQDTI	160	8						625
QLCYQDTIL	160	9	0.0001					626
QLFEDNYA	106	8						627
QLFEDNYAL	106	9	0.4600					628

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Sequence	Position	No. of Amino Acids	A*0201	A*0202	A*0203	A*0206	A*6802	SEQ ID NO.
QLFEDNYALA	106	10	0 0140	0 0065	1.1000	0.0170	0 5400	629
QLFEDNYALAV	106	11						630
QLFRNPHQA	484	9	0 0062					631
QLFRNPHQAL	484	10	0 0003					632
QLFRNPHQALL	484	11						633
QLMPYGCL	799	8						634
QLMPYGCLL	799	9	0.0230	0 0044	0.0880	0.0052	0.0031	635
QLQVFETL	396	8						636
QLQVFETLEEI	396	11						637
QLRSLTEI	141	8						638
QLRSLTEIL	141	9	0 0008					639
QMRILKET	711	8						640
QMRILKETEL	711	10	0.0001					641
QQGFFCPDPA	1027	10						642
QQKIRKYT	679	8						643
QQKIRKYTM	679	9						644
QVCTGTDM	24	8						645
QVCTGTDMKL	24	10	0 0001					646
QVFETLEEI	398	9						647
QVFETLEEIT	398	10						648
QVIRGRIL	429	8						649
QVPLQRLRI	93	9						650
QVPLQRLRIV	93	10	0 0001					651
QVRQVPLQRL	90	10	0.0001					652
QVVQGNLEL	54	9	0 0001					653
QVVQGNLELT	54	10						654
RACHPCSPM	190	9	0.0001					655
RASPLTSI	647	8						656
RASPLTSII	647	9	0.0002					657
RASPLTSIISA	647	11						658
RAVTSANI	354	8						659
RILHNGAYSL	434	10	0 0180					660
RILHNGAYSLT	434	11						661
RILKETEL	713	8						662
RILKETELRKV	713	11						663
RIVRGTQL	100	8						664
RLGSQDLL	816	8						665
RLLDIDET	868	8						666
RLLGICLT	784	8						667
RLLGICLTST	784	10						668
RLLGICLTSTV	784	11						669
RLLQETEL	689	8						670
RLLQETELV	689	9	0.0910					671
RLPASPET	34	8						672
RLPASPETHL	34	10	0.0001					673
RLPQPPICT	940	9	0 0002					674
RLPQPPICTI	940	10						675
RLRIVRGT	98	8						676
RLRIVRGTQL	98	10	0.0001					677
RLVHRDLA	840	8						678

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HER2/NEU A02 Supermotif with Binding Data

Sequence	Position	No. of Amino Acids	A*0201	A*0202	A*0203	A*0206	A*6802	SEQ ID NO.
RLVHRDLAA	840	9	0.0001					679
RMARDPQRFV	978	10	0.0020					680
RMARDPQRFVV	978	11						681
RQQKIRKYT	678	9						682
RQQKIRKYTM	678	10						683
RQVPLQRL	92	8						684
RQVPLQRLRI	92	10						685
RQVPLQRLRIV	92	11						686
RTVCAGGCA	217	9						687
RVCYGLGM	340	8						688
RVCYGLGMEHL	340	11						689
RVLQGLPREYV	545	11						690
SANIQEFA	358	8						691
SAVVGILL	656	8						692
SAVVGILLV	656	9						693
SAVVGILLVV	656	10	0.0009					694
SAVVGILLVVV	656	11						695
SAWPDSLPDL	413	10	0.0002					696
SIISAVVGI	653	9	0.0720	0.0082	0.2900	0.0130	0.2700	697
SIISAVVGIL	653	10	0.0002					698
SIISAVVGILL	653	11						699
SILRRRFT	893	8						700
SLLEDDDM	1007	8						701
SLLEDDDMGDL	1007	11						702
SLPDLSVFQNL	418	11						703
SLPTHDPSPL	1100	10	0.0059					704
SLRELGSGL	457	9	0.0002					705
SLRELGSGLA	457	10						706
SLRELGSGLAL	457	11						707
SLSFLQDI	70	8						708
SLSFLQDIQEV	70	11						709
SLTEILKGGV	144	10	0.0150					710
SLTEILKGGVL	144	11						711
SLTLQGLGI	442	9	0.0003					712
SLTRTVCA	214	8						713
SMPNPEGRYT	281	10						714
SQDLLNWCM	819	9						715
SQDLLNWCMQI	819	11						716
SQFLRGQECV	532	10						717
STDVGSCT	305	8						718
STDVGSCTL	305	9						719
STDVGSCTLV	305	10	0.0001					720
STFKGTPT	1235	8						721
STFKGTPTA	1235	9						722
STFYRSLL	1002	8						723
STQVCTGT	22	8						724
STQVCTGTDM	22	10						725
STRSGGGDL	1051	9						726
STRSGGGDLT	1051	10						727
STRSGGGDLTL	1051	11						728

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Sequence	Position	No. of Amino Acids	A*0201	A*0202	A*0203	A*0206	A*6802	SEQ ID NO.
STVQLVTQL	792	9						729
STVQLVTQLM	792	10						730
SVFQNLQV	423	8						731
SVFQNLQVI	423	9	0.0017					732
SVTCFGPEA	573	9						733
TACPYNYL	297	8						734
TACPYNYLST	297	10						735
TAENPEYL	1242	8						736
TAENPEYLGL	1242	10	0.0001					737
TANRPEDECV	496	10						738
TAPLQPEQL	389	9	0.0002					739
TAPLQPEQLQV	389	11						740
TIDVYMIM	948	8						741
TIDVYMIMV	948	9	0.0005					742
TLEEITGYL	402	9	0.0018					743
TLEEITGYLYI	402	11						744
TLERPKTL	1166	8						745
TLGLEPSEEEA	1060	11						746
TLIDTNRSRA	182	10						747
TLQGLGISWL	444	10	0.0011					748
TLSPGKNGV	1172	9	0.0002					749
TLSPGKNGVV	1172	10	0.0001					750
TLVCPLHNQEV	312	11						751
TMRRLLQET	686	9						752
TMRRLLQETEL	686	11						753
TQCVNCSQFL	526	10						754
TQLFEDNYA	105	9						755
TQLFEDNYAL	105	10						756
TQLFEDNYALA	105	11						757
TQLMPYGCL	798	9						758
TQLMPYGCLL	798	10						759
TQVCTGTDM	23	9						760
TQVCTGTDMKL	23	11						761
TVCAGGCA	218	8						762
TVPLPSET	1117	8						763
TVQLVTQL	793	8						764
TVQLVTQLM	793	9						765
TVWELMTFGA	911	10						766
TVYKGIWI	733	8						767
VAIKVLRENT	750	10						768
VARCPSGV	597	8						769
VIQNEDLGPA	988	10						770
VIRGRILHNGA	430	11						771
VLDNGDPL	116	8						772
VLDNGDPLNNT	116	11						773
VLGSGAFGT	725	9						774
VLGSGAFGTV	725	10	0.0007					775
VLGVVFGI	666	8						776
VLGVVFGIL	666	9	0.0005					777
VLGVVFGILI	666	10						778

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Sequence	Position	No. of Amino Acids	A*0201	A*0202	A*0203	A*0206	A*6802	SEQ ID NO.
VLIAIINQV	84	8						779
VLIAIINQVRQV	84	11						780
VLIQRNPQL	153	9	0 0290					781
VLQGLPREYV	546	10	0.0009					782
VLRENTSPKA	754	10						783
VLVKSPNHV	851	9	0 0002					784
VLVKSPNHVKI	851	11						785
VMAGVGSPYV	773	10	0 0180					786
VQGNLELT	56	8						787
VQGNLELTYL	56	10						788
VQGYVLIA	80	8						789
VQLVTQLM	794	8						790
VTACPYNYL	296	9						791
VTACPYNYLST	296	11						792
VTCFGPEA	574	8						793
VTGASPGGL	129	9						794
VTQLMPYGCL	797	10						795
VTQLMPYGCLL	797	11						796
VTSANIQEFA	356	10						797
VTVWELMT	910	8						798
VTVWELMTFGA	910	11						799
VTYNTDTFESM	272	11						800
VVGILLVV	658	8						801
VVGILLVVV	658	9	0.0005					802
VVGILLVVVL	658	10	0.0009					803
VVIQNEDL	987	8						804
VVIQNEDLGPA	987	11						805
VVKDVFAFGGA	1180	11						806
VVLGVVFGI	665	9	0 3500	0.0001	0.0040	0.0086	0.0200	807
VVLGVVFGIL	665	10	0 0027					808
VVLGVVFGILI	665	11						809
VVQGNLEL	55	8						810
VVQGNLELT	55	9						811
VVQGNLELTYL	55	11						812
VVVLGVVFGI	664	10	0 0032					813
VVVLGVVFGIL	664	11						814
WIPDGENV	739	8						815
WIPDGENVKI	739	10						816
WLGLRSLREL	452	10	0.0001					817
WMALESIL	888	8						818
YISAWPDSL	411	9	0.0003					819
YLEDVRLV	835	8						820
YLGLDVPV	1248	8						821
YLPTNASL	64	8						822
YLPTNASLSFL	64	11						823
YLSTDVGSCT	303	10	0.0002					824
YLSTDVGSCTL	303	11						825
YLTPQGGA	1196	8						826
YLTPQGGAA	1196	9	0.0001					827
YLYISAWPDSL	409	11						828

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Sequence	Position	No. of Amino Acids	A*0201	A*0202	A*0203	A*0206	A*6802	SEQ ID NO.
YMIMVKCWM	952	9	0 0230	0.0001	0.0160	0 0014	0.0400	829
YMIMVKCWMI	952	10	0 0600	0 0004	0 0300	0 0190	0.0011	830
YQDTILWKDI	163	10						831
YQGCQVVQGNL	50	11						832
YTFGASCV	289	8						833
YTFGASCVT	289	9						834
YTFGASCVTA	289	10						835
YTMRRLLQET	685	10						836
YVLIAHNQV	83	9	0 0005					837
YVMAGVGSPYV	772	11						838
YVNARHCL	554	8						839
YVSRLLGI	781	8						840
YVSRLLGICL	781	10	0.0004					841
YVSRLLGICLT	781	11						842

Table IX

HER2/NEU A03 Supermotif with Binding Data

Sequence	Position	No. of Amino Acids	A*0301	A*1101	A*3101	A*3301	A*6801	SEQ ID NO.
AAGCTGPK	241	8						843
AARNVLVK	847	8						844
AARPAGATLER	1159	11						845
ALESILRR	890	8						846
ALESILRRR	890	9	0.0013	0.0006				847
ALLHTANR	492	8						848
ALTLIDTNR	180	9	0.0004	0.0005				849
ALTLIDTNRSR	180	11						850
AMPNQAQMR	705	9	0.0004	0.0006				851
ASPETHLDMLR	37	11						852
ASPLDSTFYR	997	10	0.0003	0.0670	0.1200	0.0140	0.0520	853
CAAGCTGPK	240	9	0.0021	0.0021				854
CAGGCARCK	220	9	-0.0002	-0.0002				855
CLLDHVRENR	805	10	0.0003	0.0001				856
CSPMCKGSR	195	9	-0.0008	-0.0001				857
CTGTDMKLR	26	9	0.0002	0.0005				858
CTHSCVDLDDK	630	11						859
CTIDVYMIMVK	947	11						860
CVACAHYK	584	8						861
CVARCPSGVK	596	10	0.0220	0.0042	0.0008	0.0064	0.0093	862
CVNCSQFLR	528	9	0.0015	0.0310	0.5300	0.5800	0.4400	863
DLAARNVLVK	845	10	0.0018	0.0007				864
DLGMGAAK	1089	8						865
DLLEKGER	933	8						866
DLLNWCMQIAK	821	11						867
DLSYMPIWK	607	9	0.0005	0.0100	0.0002	0.0880	0.0310	868
DSECRPRFR	962	9	-0.0002	-0.0002				869
DTILWKDIFHK	165	11						870
DVRPQPPSPR	1144	10	0.0003	0.0001				871
DVYMIMVK	950	8						872
EILKGGVLIQR	147	11						873
EIPDLLEK	930	8						874
EIPDLLEKGER	930	11						875
ELMTFGAK	914	8						876
ELVSEFSR	971	8						877
ELVSEFSRMAR	971	11						878
ESMPNPEGR	280	9	0.0003	-0.0002				879
ESSEDCQSLTR	207	11						880
ETELRKVK	717	8						881
ETEYHADGGK	874	10	0.0003	0.0001				882
ETHLDMLR	40	8						883
EVTAEDGTQR	321	10	0.0002	0.0001				884
FSRMARDPQR	976	10	-0.0002	0.0010				885
GAFGTVYK	729	8						886
GAGGMVHHR	1038	9	-0.0002	0.0043				887
GAGGMVHHRHR	1038	11						888
GAKPYDGIPAR	919	11						889
GAMPNQAQMR	704	10	-0.0002	0.0041				890
GAPPSTFK	1231	8						891
GASPGGLR	131	8						892

Table IX

HER2/NEU A03 Supermotif with Binding Data

Sequence	Position	No. of Amino Acids	A*0301	A*1101	A*3101	A*3301	A*6801	SEQ ID NO.
GATLERPK	1164	8						893
GILIKRRQQK	672	10	0 0150	0 0014				894
GISWLGLR	449	8						895
GISWLGLRSLR	449	11						896
GIWIPDGENVK	737	11						897
GLACHQLCAR	508	10	0.0110	0.0001				898
GLEPSEEEAPR	1062	11						899
GLGISWLGLR	447	10	0 0037	0.0001				900
GLGMEHLR	344	8						901
GLGMEHLREVR	344	11						902
GLPREYVNAR	549	10	0 0002	0.0003				903
GLRELQLR	136	8						904
GMEHLREVR	346	9	-0.0002	-0.0002				905
GMSYLEDVR	832	9	-0.0002	0.0002				906
GMVHHRHR	1041	8						907
GSGAFGTVYK	727	10	0.0660	0 1300	0 0014	-0.0013	0.0012	908
GTQRCEKCSK	327	10	0.0210	0.6100	0 0140	0.0012	0.0100	909
GVGSPYVSR	776	9	0.0010	0 0066				910
GVVFGILIK	668	9	0.0047	0.0890	0.0019	0.0025	0.0011	911
GVVFGILIKR	668	10	0.0180	0.0330	0 0590	0.0140	0.4300	912
GVVFGILIKRR	668	11						913
HADGGKVPIK	878	10	0 0003	0.0008				914
HSCVDLDDK	632	9	-0.0002	0.0007				915
HTVPWDQLFR	478	10	0.0035	0.0720	0 9600	0.3300	2.0000	916
HVKITDFGLAR	858	11						917
HVRENRGR	809	8						918
ILIKRRQQK	673	9	0.3800	0.0097	0.0760	0.0064	0.0001	919
ILIKRRQQKIR	673	11						920
ILKETELR	714	8						921
ILKETELRK	714	9	0.0190	0.0023	0 0009	0.0010	0.0001	922
ILKETELRKVK	714	11						923
ILKGGVLIQR	148	10	0.0400	0 0005	0.7300	0.2400	0.0390	924
ILWKDIFHK	167	9	0.2800	0 3100	0.2200	0.0300	0.0046	925
ISWLGLRSLR	450	10	0.0410	0 0027	2 6000	0.1300	0.1100	926
ITDFGLAR	861	8						927
KIPVAIKVLR	747	10	0 0009	0 0099				928
KIRKYTMR	681	8	0.0010	0 0004				929
KIRKYTMRR	681	9	0.7600	0.0018	1.1000	0.0072	0.0002	930
KITDFGLAR	860	9	0 1700	0 2400	0.1800	0.0012	0.0049	931
KVLRENTSPK	753	10	0.3800	0.2200	0.0068	0.0012	0.0008	932
LAARNVLVK	846	9	0 0580	0 0285	-0.0005	-0.0012	0.0160	933
LACHQLCAR	509	9	-0 0002	0.0003				934
LALTLIDTNR	179	10	-0 0002	0 0003				935
LIAIINQVR	85	8						936
LIDTNRSR	183	8						937
LIKRRQQK	674	8						938
LIKRRQQKIR	674	10	0 0002	0 0001				939
LIKRRQQKIRK	674	11						940
LLDHVRENR	806	9	0 0370	0 0006	0 0360	0 0890	0.0014	941
LLDHVRENRGR	806	11						942

Table IX

HER2/NEU A03 Supermotif with Binding Data

Sequence	Position	No. of Amino Acids	A*0301	A*1101	A*3101	A*3301	A*6801	SEQ ID NO.
LLNWCMQIAK	822	10	0.1400	0 1400	0 0100	0.0088	0.0086	943
LSPGKNGVVK	1173	10	-0 0002	0 0003				944
LSVFQNLQVIR	422	11						945
LSYMPIWK	608	8						946
LTLIDTNR	181	8						947
LTLIDTNRSR	181	10	0 0002	0 0005				948
LVHRDLAAR	841	9	0.0040	0.0014				949
LVKSPNHVK	852	9	0 4800	0 0700	0.0990	0 0370	0.1100	950
LVSEFSRMAR	972	10	0.0072	0.0330	0.3700	0.2300	0.2200	951
MAGVGSPYVSR	774	11						952
MALESILR	889	8						953
MALESILRR	889	9	0.0034	0 0237	0.0940	0.2200	0.0630	954
MALESILRRR	889	10	0.0011	0 0003				955
MIDSECRPR	960	9	0.0017	0.0006				956
MIDSECRPRFR	960	11						957
MSYLEDVR	833	8						958
NIQEFAGCK	360	9	0 0002	0.0036				959
NIQEFAGCKK	360	10	0 0003	0.0056				960
NLQVIRGR	427	8						961
NTSPKANK	758	8						962
NVKIPVAIK	745	9	0.0058	0 0007	0.0015	0.0820	0.1200	963
NVLVKSPNHVK	850	11						964
PAGATLER	1162	8						965
PAGATLERPK	1162	10	-0.0002	-0 0002				966
PAREIPDLLEK	927	11						967
PASPLDSTFYR	996	11						968
PLDSTFYR	999	8						969
PLQRLRIVR	95	9	0.0002	0.0001				970
PSEEEAPR	1065	8						971
PTHDPSPLQR	1102	10	0 0003	0 0001				972
PVAIKVLR	749	8						973
PVTGASPGGLR	128	11						974
QALLHTANR	491	9	0.0046	0.0010				975
QAQMRILK	709	8						976
QLALTLIDTNR	178	11						977
QLCYQDTILWK	160	11						978
QLRSLTEILK	141	10	0.2000	0.0130	0 0270	0.0047	0.0002	979
QMRILKETELR	711	11						980
QVCTGTDMK	24	9	0.0007	0.0520	0.0002	0.0006	0.0110	981
QVCTGTDMKLR	24	11						982
QVPLQRLR	93	8						983
QVPLQRLRIVR	93	11						984
QVRQVPLQR	90	9	0.0029	0 0005				985
QVRQVPLQRLR	90	11						986
RACHPCSPMCK	190	11						987
RILKETELR	713	9	0.0007	0 0038				988
RILKETELRK	713	10	0.0570	0 1100	0 0055	0.0013	0.0002	989
RLVHRDLAAR	840	10	0.1800	0.0001	0.9500	0.0021	0.0036	990
RMARDPQR	978	8						991
RSLTEILK	143	8						992

Table IX

HER2/NEU A03 Supermotif with Binding Data

Sequence	Position	No. of Amino Acids	A*0301	A*1101	A*3101	A*3301	A*6801	SEQ ID NO.
RTVCAGGCAR	217	10	0.0068	0.0130	0.4500	0 0220	0.0250	993
RVLQGLPR	545	8						994
SANIQEFAGCK	358	11						995
SMPNPEGR	281	8						996
SSEDCQSLTR	208	10	-0.0002	0 0020				997
STQVCTGTDMK	22	11						998
SVFQNLQVIR	423	10	0.0170	0.0750	0 0340	0 0390	0.2500	999
TAEDGTQR	323	8						1000
TAEDGTQRCEK	323	11						1001
TIDVYMIMVK	948	10	0 0130	0.1200	0.0018	0.0120	0.0250	1002
TILWKDIFHK	166	10	0.0430	3 6000	0 0370	0.0420	0.0400	1003
TLIDTNRSR	182	9	0 0004	0 0005				1004
TLSPGKNGVVK	1172	11						1005
TVCAGGCAR	218	9	0.0004	0 0230	0 1400	0 0890	0.0970	1006
TVCAGGCARCK	218	11						1007
TVPWDQLFR	479	9	0 0006	0 0072				1008
TVWELMTFGAK	911	11						1009
VARCPSGVK	597	9	0.0100	-0 0002				1010
VLGVVFGILIK	666	11						1011
VLIAHNQVR	84	9	0.0033	0 0007				1012
VLRENTSPK	754	9	0.4000	0 0130	0.1400	0.1000	0.0001	1013
VLVKSPNHVK	851	10	0 0820	0.0072	0.0052	0.0032	0.0005	1014
VSEFSRMAR	973	9	-0 0002	0 0021				1015
VTAEDGTQR	322	9	0 0002	0 0140	0 0011	0.0037	0.1000	1016
VTGASPGGLR	129	10	0.0002	0.0005				1017
VVFGILIK	669	8						1018
VVFGILIKR	669	9	0.1100	0.7200	1.4000	0.3700	2 0000	1019
VVFGILIKRR	669	10	0 0030	0 0160	0 0620	0 1500	0.5400	1020
WIPDGENVK	739	9	0 0002	0 0001				1021
WLGLRSLR	452	8						1022
WMALESILR	888	9	-0 0002	-0 0002				1023
WMALESILRR	888	10	0.0085	0 0016				1024
WMALESILRRR	888	11						1025
WMIDSECR	959	8						1026
WMIDSECRPR	959	10	-0 0002	0 0002				1027
YLEDVRLVHR	835	10	0 0003	0 0001				1028
YVLIAHNQVR	83	10	0.0043	0 0013				1029
YVNQPDVR	1139	8						1030

Table X
HER2/NEU A24 Supermotif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*2401	SEQ ID NO.
AFDNLYYW	1216	8	0.0039	1031
AFGGAVENPEY	1186	11		1032
AFGTVYKGI	730	9	0.0002	1033
AFGTVYKGIW	730	10	0.0010	1034
AFGTVYKGIWI	730	11	0.0008	1035
AFSPAFDNL	1212	9	0.0011	1036
AFSPAFDNLY	1212	10		1037
AFSPAFDNLYY	1212	11		1038
ALAVLDNGDPL	113	11		1039
ALCRWGLL	5	8		1040
ALCRWGLLL	5	9		1041
ALCRWGLLLAL	5	11		1042
ALESILRRRF	890	10		1043
ALHHHNTHL	466	9		1044
ALHHHNTHLCF	466	11		1045
ALVTYNTDTF	270	10		1046
AMPNQAQM	705	8		1047
AMPNQAQMRI	705	10	0.0002	1048
AMPNQAQMRIL	705	11	-0.0003	1049
ATLERPKTL	1165	9		1050
AVENPEYL	1190	8		1051
AVLDNGDPL	115	9		1052
AVTSANIQEF	355	10		1053
AVVGILLVVVL	657	11		1054
AWPDSLPDL	414	9	0.0041	1055
AYSLTLQGL	440	9	0.1300	1056
AYSLTLQGLGI	440	11	0.0230	1057
AYVMAGVGSPY	771	11		1058
CFVHTVPW	475	8	0.0190	1059
CFVHTVPWDQL	475	11	0.0003	1060
CLHFNHSGI	255	9		1061
CLTSTVQL	789	8		1062
CMQIAKGM	826	8		1063
CMQIAKGMSY	826	10		1064
CMQIAKGMSYL	826	11	-0.0003	1065
CTGPKHSDCL	244	10		1066
CTGTDMKL	26	8		1067
CTGTDMKLRL	26	10		1068
CTHSCVDL	630	8		1069
CTIDVYMI	947	8		1070
CTIDVYMIM	947	9		1071
CVEECRVL	540	8		1072
CVEECRVLQGL	540	11		1073
CVGEGLACHQL	504	11		1074
CVNCSQFL	528	8		1075
CVTACPYNY	295	9		1076
CVTACPYNYL	295	10		1077
CYGLGMEHL	342	9	0.0180	1078
CYQDTILW	162	8	0.0120	1079
CYQDTILWKDI	162	11	0.0016	1080

Table X

HER2/NEU A24 Supermotif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*2401	SEQ ID NO.
DFGLARLL	863	8	0.0005	1081
DFGLARLLDI	863	10	0.0002	1082
DIFHKNNQL	171	9		1083
DIFHKNNQLAL	171	11		1084
DIQEVQGY	76	8		1085
DIQEVQGYVL	76	10		1086
DIQEVQGYVLI	76	11		1087
DLAARNVL	845	8		1088
DLGMGAAKGL	1089	10		1089
DLGPASPL	993	8		1090
DLLEKGERL	933	9		1091
DLLNWCMQI	821	9		1092
DLSVFQNL	421	8		1093
DLSVFQNLQVI	421	11		1094
DLSYMPIW	607	8		1095
DLSYMPIWKF	607	10		1096
DLVDAEEY	1016	8		1097
DLVDAEEYL	1016	9		1098
DMGDLVDAEEY	1013	11		1099
DTILWKDI	165	8		1100
DTILWKDIF	165	9		1101
DVFDGDLGM	1084	9		1102
DVGSCTLVCPL	307	11		1103
DVRLVHRDL	838	9		1104
DVWSYGVTVW	904	10		1105
DVYMIMVKCW	950	10		1106
DVYMIMVKCWM	950	11		1107
EFAGCKKI	363	8	-0.0003	1108
EFAGCKKIF	363	9	0.0003	1109
EILDEAYVM	766	9		1110
EILKGGVL	147	8		1111
EILKGGVLI	147	9		1112
EITGYLYI	405	8		1113
EITGYLYISAW	405	11		1114
ELAALCRW	2	8		1115
ELAALCRWGL	2	10		1116
ELAALCRWGLL	2	11		1117
ELGSGLAL	460	8		1118
ELGSGLALI	460	9		1119
ELHCPALVTY	265	10		1120
ELMTFGAKPY	914	10		1121
ELQLRSLTEI	139	10		1122
ELQLRSLTEIL	139	11		1123
ELRKVKVL	719	8		1124
ELTYLPTNASL	61	11		1125
ELVSEFSRM	971	9		1126
ETDGYVAPL	1123	9		1127
ETELRKVKVL	717	10		1128
ETELVEPL	693	8		1129
ETHLDMLRHL	40	10		1130

Table X

HER2/NEU A24 Supermotif Peptides with Binding Data

Sequence	Position	No of Amino Acids	A*2401	SEQ ID NO.
ETHLDMLRHLY	40	11		1131
ETLEEITGY	401	9		1132
ETLEEITGYL	401	10		1133
ETLEEITGYLY	401	11		1134
EVQGYVLI	79	8		1135
EVRAVTSANI	352	10		1136
EYHADGGKVPI	876	11	-0.0003	1137
EYLVPQQGF	1022	9	0.0014	1138
EYLVPQQGFF	1022	10	0 0120	1139
EYVNARHCL	553	9	0.0061	1140
FLQDIQEVQGY	73	11		1141
FTHQSDVW	899	8		1142
FTHQSDVWSY	899	10		1143
FVHTVPWDQL	476	10		1144
FVHTVPWDQLF	476	11		1145
FVVIQNEDL	986	9		1146
FYRSLLEDDDM	1004	11		1147
GICELHCPAL	262	10		1148
GICLTSTVQL	787	10		1149
GILIKRRQQKI	672	11		1150
GILLVVVL	660	8		1151
GIPAREIPDL	925	10		1152
GIPAREIPDLL	925	11		1153
GISWLGLRSL	449	10		1154
GLALHHINTHL	464	11		1155
GLARLLDI	865	8		1156
GLGISWLGL	447	9		1157
GLRELQLRSL	136	10		1158
GLRSLREL	454	8		1159
GMGAAKGL	1091	8	-0.0003	1160
GMGAAKGLQSL	1091	11	-0.0003	1161
GMSYLEDVRL	832	10		1162
GTDMKLRL	28	8		1163
GTPTAENPEY	1239	10		1164
GTPTAENPEYL	1239	11		1165
GTQLFEDNY	104	9		1166
GTQLFEDNYAL	104	11		1167
GTVYKGIW	732	8		1168
GTVYKGIWI	732	9		1169
GVGSPYVSRL	776	10		1170
GVGSPYVSRLL	776	11		1171
GVKPDLSY	603	8		1172
GVKPDLSYM	603	9		1173
GVKPDLSYMPI	603	11		1174
GVLIQRNPQL	152	10		1175
GVTVWELM	909	8		1176
GVTVWELMTF	909	10		1177
GVVFGILI	668	8		1178
GVVKDVFAF	1179	9		1179
GYLYISAW	408	8	0 0044	1180

Table X

HER2/NEU A24 Supermotif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*2401	SEQ ID NO.
HFNHSGICEL	257	10	0 0002	1181
HLCFVHTVPW	473	10		1182
HLDMLRHL	42	8		1183
HLDMLRHLY	42	9		1184
HTVPWDQL	478	8		1185
HTVPWDQLF	478	9		1186
HVKITDFGL	858	9		1187
HVRENRGRL	809	9		1188
IFGSLAFL	370	8	0.0120	1189
IFHKNNQL	172	8	-0 0003	1190
IFHKNNQLAL	172	10	0.0022	1191
IISAVVGI	654	8		1192
IISAVVGIL	654	9		1193
IISAVVGILL	654	10		1194
ILDEAYVM	767	8		1195
ILHNGAYSL	435	9		1196
ILHNGAYSLTL	435	11		1197
ILIKRRQQKI	673	10		1198
ILKGGVLI	148	8		1199
ILLVVVLGVVF	661	11		1200
IMVKCWMI	954	8	0.0210	1201
ITDFGLARL	861	9		1202
ITDFGLARLL	861	10		1203
ITGYLYISAW	406	10		1204
IVRGTQLF	101	8		1205
IWIPDGENVKI	738	11	0 0027	1206
KIFGSLAF	369	8		1207
KIFGSLAFL	369	9		1208
KIPVAIKVL	747	9		1209
KIRKYTMRRL	681	10		1210
KIRKYTMRRLL	681	11		1211
KITDFGLARL	860	10		1212
KITDFGLARLL	860	11		1213
KVKVLGSGAF	722	10		1214
KVLGSGAF	724	8		1215
KVPIKWMAL	883	9		1216
KWMALESI	887	8	0.0080	1217
KWMALESIL	887	9	0.0150	1218
KYTMRRLL	684	8	0.0024	1219
LFEDNYAL	107	8	0.0006	1220
LFEDNYALAVL	107	11	0 0006	1221
LFRNPHQAL	485	9	0.0002	1222
LFRNPHQALL	485	10	0.0014	1223
LIHHNTHL	467	8		1224
LIHHNTHLCF	467	10		1225
LIKRRQQKI	674	9		1226
LIQRNPQL	154	8		1227
LIQRNPQLCY	154	10		1228
LLDIDETEY	869	9		1229
LLEDDDMGDL	1008	10		1230

Table X

HER2/NEU A24 Supermotif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*2401	SEQ ID NO.
LLEKGFRL	934	8		1231
LLNWCMQI	822	8		1232
LLQETELVEPL	690	11		1233
LLVVVLGVVF	662	10		1234
LMPYGCLL	800	8	0.0076	1235
LMTFGAKPY	915	9	0.0001	1236
LTCSPQPEY	1131	9		1237
LTEILKGGVL	145	10		1238
LTEILKGGVLI	145	11		1239
LTLQGLGI	443	8		1240
LTLQGLGISW	443	10		1241
LTLQGLGISWL	443	11		1242
LTSHSAVVGI	651	11		1243
LTSTVQLVTQL	790	11		1244
LTYLPTNASL	62	10		1245
LVDAEEYL	1017	8		1246
LVEPLTPSGAM	696	11		1247
LVKSPNHVKI	852	10		1248
LVPQQGFF	1024	8		1249
LVSEFSRM	972	8		1250
LVTQLMPY	796	8		1251
LVTQLMPYGCL	796	11		1252
LVTYNTDTF	271	9		1253
LVVVLGVVF	663	9		1254
LVVVLGVVFGI	663	11		1255
LYISAWPDSL	410	10	0.0840	1256
MIDSECRPRF	960	10		1257
MIMVKCWM	953	8		1258
MIMVKCWMI	953	9		1259
MTFGAKPY	916	8		1260
MTFGAKPYDGI	916	11		1261
NIQEFAGCKKI	360	11		1262
NLQVIRGRI	427	9		1263
NLQVIRGRIL	427	10		1264
NTAPLQPEQL	388	10		1265
NTDTFESM	275	8		1266
NTSPKANKEI	758	10		1267
NTSPKANKEIL	758	11		1268
NVKIPVAI	745	8		1269
NVKIPVAIKVL	745	11		1270
NWCMQIAKGM	824	10	0.0002	1271
PICTIDVY	945	8		1272
PICTIDVYM	945	9		1273
PICTIDVYMI	945	10		1274
PICTIDVYMIM	945	11		1275
PIKWMALESI	885	10		1276
PIKWMALESIL	885	11		1277
PINCTHSCVDL	627	11		1278
PLDSTFYRSL	999	10		1279
PLDSTFYRSLL	999	11		1280

Table X
HER2/NEU A24 Supermotif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*2401	SEQ ID NO.
PLPSETDGY	1119	9		1281
PLQPEQLQVF	391	10		1282
PLTCSPQPEY	1130	10		1283
PLTPSGAM	699	8		1284
PMCKGSRCW	197	9	0.0011	1285
PTAENPEY	1241	8		1286
PTAENPEYL	1241	9		1287
PTAENPEYLGL	1241	11		1288
PTHDPSPL	1102	8		1289
PTHDPSPLQRY	1102	11		1290
PTNASLSF	66	8		1291
PTNASLSFL	66	9		1292
PTQCVNCSQF	525	10		1293
PTQCVNCSQFL	525	11		1294
PVTGASPGGL	128	10		1295
PYDGIPAREI	922	10	0.0005	1296
PYVSRLLGI	780	9	0.1700	1297
PYVSRLLGICL	780	11	0.0320	1298
QIAKGMSY	828	8		1299
QIAKGMSYL	828	9		1300
QLCARGHCW	513	9		1301
QLCYQDTI	160	8		1302
QLCYQDTIL	160	9		1303
QLCYQDTILW	160	10		1304
QLFEDNYAL	106	9		1305
QLFRNPHQAL	484	10		1306
QLFRNPHQALL	484	11		1307
QLMPYGCL	799	8		1308
QLMPYGCLL	799	9		1309
QLQVFETL	396	8		1310
QLQVFETLEEI	396	11		1311
QLRSLTEI	141	8		1312
QLRSLTEIL	141	9		1313
QLVTQLMPY	795	9		1314
QMRILKETEL	711	10		1315
QVCTGTDM	24	8		1316
QVCTGTDMKL	24	10		1317
QVFETLEEI	398	9		1318
QVIRGRIL	429	8		1319
QVPLQRLRI	93	9		1320
QVRQVPLQRL	90	10		1321
QVVQGNLEL	54	9		1322
QVVQGNLELTY	54	11		1323
RFRELVSEF	968	9	0.0180	1324
RFTHQSDVW	898	9	0.0110	1325
RFTHQSDVWSY	898	11		1326
RFVVIQNEDL	985	10	0.0002	1327
RILHNGAY	434	8		1328
RILHNGAYSL	434	10		1329
RILKETEL	713	8		1330

Table X

HER2/NEU A24 Supermotif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*2401	SEQ ID NO.
RIVRGTQL	100	8		1331
RIVRGTQLF	100	9		1332
RLGSQDLL	816	8		1333
RLGSQDLLNW	816	10		1334
RLLDIDETEY	868	10		1335
RLLQETEL	689	8		1336
RLPASPETHL	34	10		1337
RLPQPPICTI	940	10		1338
RLRIVRGTQL	98	10		1339
RLRIVRGTQLF	98	11		1340
RMARDPQRF	978	9	0.0032	1341
RVCYGLGM	340	8		1342
RVCYGLGMEHL	340	11		1343
RVLQGLPREY	545	10		1344
RWGLLLAL	8	8	0.0250	1345
RWGLLLALL	8	9	1.3000	1346
RYSEDPTVPL	1111	10	0.0120	1347
SHSAVVGI	653	9		1348
SHSAVVGIL	653	10		1349
SHSAVVGILL	653	11		1350
SLAFLPESF	373	9		1351
SLLEDDDM	1007	8		1352
SLLEDDDMGDL	1007	11		1353
SLPDLSVF	418	8		1354
SLPDLSVFQNL	418	11		1355
SLPTHDPSPL	1100	10		1356
SLRELGSGL	457	9		1357
SLRELGSGLAL	457	11		1358
SLSFLQDI	70	8		1359
SLTEILKGGVL	144	11		1360
SLTLQGLGI	442	9		1361
SLTLQGLGISW	442	11		1362
SMPNPEGRY	281	9	0.0001	1363
SMPNPEGRYTF	281	11	0.0180	1364
STDVGSCTL	305	9		1365
STFYRSLL	1002	8		1366
STQVCTGTDM	22	10		1367
STRSGGGDL	1051	9		1368
STRSGGGDLTL	1051	11		1369
STVQLVTQL	792	9		1370
STVQLVTQLM	792	10		1371
SVFQNLQVI	423	9		1372
SWLGLRSL	451	8	-0.0003	1373
SWLGLRSLREL	451	11	0.0036	1374
SYGVTVWEL	907	9	0.1200	1375
SYGVTVWELM	907	10	0.0630	1376
SYLEDVRL	834	8	0.0059	1377
SYMPIWKF	609	8	0.3200	1378
TFGAKPYDGI	917	10	0.0002	1379
TIDVYMIM	948	8		1380

Table X
HER2/NEU A24 Supermotif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*2401	SEQ ID NO.
TILWKDIF	166	8		1381
TLEEITGY	402	8		1382
TLEEITGYL	402	9		1383
TLEEITGYLY	402	10		1384
TLEEITGYLYI	402	11		1385
TLERPKTL	1166	8		1386
TLQGLGISW	444	9		1387
TLQGLGISWL	444	10		1388
TMRRLLQETEL	686	11	-0.0003	1389
TVPLPSETDGY	1117	11		1390
TVPWDQLF	479	8		1391
TVQLVTQL	793	8		1392
TVQLVTQLM	793	9		1393
TVQLVTQLMPY	793	11		1394
TVWELMTF	911	8		1395
TVYKGIWI	733	8		1396
TYLPTNASL	63	9	0.0380	1397
TYLPTNASLSF	63	11	8.9000	1398
TYNTDTFESM	273	10	0.0074	1399
VFDGDLGM	1085	8		1400
VFETLEEI	399	8	-0.0003	1401
VFETLEEITGY	399	11		1402
VFQNLQVI	424	8	-0.0003	1403
VLDNGDPL	116	8		1404
VLGSGAFGTVY	725	11		1405
VLGVVFGI	666	8		1406
VLGVVFGIL	666	9		1407
VLGVVFGILI	666	10		1408
VLIQRNPQL	153	9		1409
VLIQRNPQLCY	153	11		1410
VLQGLPREY	546	9		1411
VLVKSPNHVKI	851	11		1412
VMAGVGSPY	773	9	0.0001	1413
VTACPYNY	296	8		1414
VTACPYNYL	296	9		1415
VTGASPGGL	129	9		1416
VTQLMPYGCL	797	10		1417
VTQLMPYGCLL	797	11		1418
VTSANIQEF	356	9		1419
VTVWELMTF	910	9		1420
VTYNTDTF	272	8		1421
VTYNTDTFESM	272	11		1422
VVGILLVVVL	658	10		1423
VVIQNEDL	987	8		1424
VVKDVFAF	1180	8		1425
VVLGVVFGI	665	9		1426
VVLGVVFGIL	665	10		1427
VVLGVVFGILI	665	11		1428
VVQGNLEL	55	8		1429
VVQGNLELTY	55	10		1430

Table X
HER2/NEU A24 Supermotif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*2401	SEQ ID NO.
VVQGNLELTYL	55	11		1431
VVVLGVVF	664	8		1432
VVVLGVVFGI	664	10		1433
VVVLGVVFGIL	664	11		1434
VWSYGVTVW	905	9	0.0800	1435
VWSYGVTVWEL	905	11	0 0920	1436
VYMIMVKCW	951	9	0.1600	1437
VYMIMVKCWM	951	10	0.0220	1438
VYMIMVKCWMI	951	11	1.8000	1439
WIPDGENVKI	739	10		1440
WLGLRSLREL	452	10		1441
WMALESIL	888	8	-0.0003	1442
WMIDSECRPRF	959	11	0.0011	1443
YISAWPDSL	411	9		1444
YLPTNASL	64	8		1445
YLPTNASLSF	64	10		1446
YLPTNASLSFL	64	11		1447
YLSTDVGSCTL	303	11		1448
YLVPQQGF	1023	8		1449
YLVPQQGFF	1023	9		1450
YLYISAWPDSL	409	11		1451
YMIMVKCW	952	8	0.0009	1452
YMIMVKCWM	952	9		1453
YMIMVKCWMI	952	10	0.0019	1454
YVMAGVGSPY	772	10	0 0001	1455
YVNARHCL	554	8		1456
YVSRLLGI	781	8		1457
YVSRLLGICL	781	10		1458

Table XI
HER2/NEU B07 Supermotif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	B*0702	SEQ ID NO.
APGAGGMV	1036	8	0.0063	1459
APLQPEQL	390	8	-0.0006	1460
APLQPEQLQV	390	10	0.0001	1461
APLQPEQLQVF	390	11	0.0011	1462
APLTCSPQPEY	1129	11	-0.0002	1463
APQPHPPPA	1204	9	0 0056	1464
APQPHPPPAF	1204	10	0.0530	1465
APSEGAGSDV	1076	10	0.0002	1466
APSEGAGSDVF	1076	11	0.0006	1467
CPAEQRASPL	642	10	0.1500	1468
CPDPAPGA	1032	8	-0.0002	1469
CPDPAPGAGGM	1032	11	-0.0002	1470
CPINCTHSCV	626	10	0.0002	1471
CPLHNQEV	315	8	-0 0006	1472
CPLHNQEVTA	315	10	0.0001	1473
CPSGVKPDL	600	9	0 0140	1474
CPSGVKPDLSY	600	11	0.0300	1475
CPYNYLSTDV	299	10	0 0016	1476
DPAPGAGGM	1034	9	0.0001	1477
DPAPGAGGMV	1034	10	0.0002	1478
DPASNTAPL	384	9	0 0004	1479
DPLNNTTPV	121	9	0 0002	1480
DPQRFVVI	982	8	-0 0006	1481
DPSPLQRY	1105	8	-0.0006	1482
EPLTPSGA	698	8	-0 0002	1483
EPLTPSGAM	698	9	0 0110	1484
GPASPLDSTF	995	10	0 0510	1485
GPASPLDSTFY	995	11	0.0036	1486
GPEADQCV	578	8	-0 0006	1487
GPEADQCVA	578	9	0 0001	1488
GPEADQCVACA	578	11	-0.0003	1489
GPGPTQCV	522	8	-0 0006	1490
GPKHSDCL	246	8	0 0092	1491
GPKHSDCLA	246	9	0 0001	1492
GPKHSDCLACL	246	11	0.0006	1493
GPLPAARPA	1155	9	0 0900	1494
GPLPAARPAGA	1155	11	0 0160	1495
GPTQCVNCSQF	524	11	0.0005	1496
HPECQPQNGSV	564	11	-0 0002	1497
HPPPAFSPA	1208	9	0.0093	1498
HPPPAFSPAF	1208	10	0 0018	1499
IPAREIPDL	926	9	0 0006	1500
IPAREIPDLL	926	10	0 0004	1501
IPDGENVKI	740	9	0 0001	1502
IPDGENVKIPV	740	11	0.0023	1503
IPDLLEKGERL	931	11	-0.0002	1504
IPVAIKVL	748	8	0.0120	1505
KPCARVCY	336	8	-0.0006	1506
KPCARVCYGL	336	10	0.0370	1507
KPDLSYMPI	605	9	0 0720	1508

Table XI

HER2/NEU B07 Supermotif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	B*0702	SEQ ID NO.
KPDLSYMPIW	605	10	0 0001	1509
KPYDGIPA	921	8	0.0150	1510
KPYDGIPAREI	921	11	0.0430	1511
LPAARPAGA	1157	9	0.0027	1512
LPAARPAGATL	1157	11	0.0140	1513
LPASPETHL	35	9	0.0002	1514
LPASPETHLDM	35	11	-0.0002	1515
LPDLSVFQNL	419	10	0.0003	1516
LPESFDGDPA	377	10	0.0001	1517
LPPGAASTQV	16	10	0.0002	1518
LPQPPICTI	941	9	0.0280	1519
LPQPPICTIDV	941	11	0.0032	1520
LPREYVNA	550	8	0.0012	1521
LPSETDGY	1120	8	-0.0006	1522
LPSETDGYV	1120	9	0.0002	1523
LPSETDGYVA	1120	10	0 0001	1524
LPTDCCHEQCA	231	11	-0.0003	1525
LPTHDPSPL	1101	9	0 0460	1526
LPTNASLSF	65	9	0.0260	1527
LPTNASLSFL	65	10	0 0190	1528
MPNPEGRY	282	8	-0.0006	1529
MPNPEGRYTF	282	10	0 0001	1530
MPNQAQMRI	706	9	0.0090	1531
MPNQAQMRIL	706	10	0 0490	1532
MPYGCLLDHV	801	10	0.0085	1533
NPEGRYTF	284	8	-0 0002	1534
NPEGRYTFGA	284	10	0 0001	1535
NPEYLGLDV	1245	9	0.0001	1536
NPEYLGLDVPV	1245	11	-0 0002	1537
NPEYLTPQGGA	1193	11	-0.0003	1538
NPHQALLHTA	488	10	0.0005	1539
NPQLCYQDTI	158	10	0.0001	1540
NPQLCYQDTIL	158	11	-0.0002	1541
PPAFSPAF	1210	8	-0.0002	1542
PPAFSPAFDNL	1210	11	-0 0002	1543
PPERGAPPSTF	1227	11	-0 0003	1544
PPGAASTQV	17	9	0.0001	1545
PPICTIDV	944	8	-0 0006	1546
PPICTIDVY	944	9	0.0001	1547
PPICTIDVYM	944	10	0.0004	1548
PPICTIDVYMI	944	11	0.0064	1549
PPPAFSPA	1209	8	-0.0002	1550
PPPAFSPAF	1209	9	0.0002	1551
PPSPREGPL	1149	9	0 0054	1552
PPSPREGPLPA	1149	11	0 4500	1553
PPSTFKGTPTA	1233	11	-0.0003	1554
QPEQLQVF	393	8	-0 0002	1555
QPEQLQVFETL	393	11	-0 0002	1556
QPEYVNQPDV	1136	10	0.0001	1557
QPHPPPAF	1206	8	0 0002	1558

Table XI
HER2/NEU B07 Supermotif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	B*0702	SEQ ID NO.
QPHPPPAFSPA	1206	11	0.0003	1559
QPPICTIDV	943	9	0 0001	1560
QPPICTIDVY	943	10	0.0001	1561
QPPICTIDVYM	943	11	0.0020	1562
QPPSPREGPL	1148	10	0 0014	1563
QPQNGSVTCF	568	10	0 0004	1564
RPEDECVGEGL	499	11	-0.0002	1565
RPRFRELV	966	8	0.0410	1566
RPRFRELVSEF	966	11	1 3000	1567
SPAFDNLY	1214	8	-0.0002	1568
SPAFDNLYY	1214	9	0.0001	1569
SPAFDNLYYW	1214	10	0.0001	1570
SPETHLDM	38	8	0.0014	1571
SPETHLDML	38	9	0 0005	1572
SPGGLREL	133	8	0 0550	1573
SPGGLRELQL	133	10	0 0580	1574
SPGKNGVV	1174	8	0.0230	1575
SPGKNGVVKDV	1174	11	-0.0002	1576
SPKANKEI	760	8	0.0580	1577
SPKANKEIL	760	9	0.1200	1578
SPLAPSEGA	1073	9	0.0030	1579
SPLDSTFY	998	8	-0.0006	1580
SPLDSTFYRSL	998	11	0.0640	1581
SPLTSIISA	649	9	0 0150	1582
SPLTSIISAV	649	10	0 0900	1583
SPLTSIISAVV	649	11	0.0250	1584
SPMCKGSRCW	196	10	0.0021	1585
SPNHVKITDF	855	10	0.0016	1586
SPREGPLPA	1151	9	0.6400	1587
SPREGPLPAA	1151	10	0.4600	1588
SPYVSRLL	779	8	0.0440	1589
SPYVSRLLGI	779	10	0.1000	1590
TPSGAMPNQA	701	10	0.0001	1591
TPTAENPEY	1240	9		1592
TPTAENPEYL	1240	10	0.0002	1593
TPVTGASPGGL	127	11	-0.0002	1594
VPIKWMAL	884	8	1 4000	1595
VPIKWMALESI	884	11	0.0017	1596
VPLPSETDGY	1118	10	0 0001	1597
VPLPSETDGYV	1118	11	-0.0002	1598
VPLQRLRI	94	8	0.0020	1599
VPLQRLRIV	94	9	0.0077	1600
WPDSLPDL	415	8	0.0200	1601
WPDSLPDLSV	415	10	0 0044	1602
WPDSLPDLSVF	415	11	0 0005	1603

Table XII
HER2/NEU B27 Supermotif Peptides

Sequence	Position	No. of Amino Acids	SEQ ID NO.
AHNQVRQVPL	87	10	1604
AHYKDPPF	588	8	1605
ARCPSGVKPDL	598	11	1606
ARDPQRFVVI	980	10	1607
AREIPDLL	928	8	1608
ARLLDIDETEY	867	11	1609
ARPAGATL	1160	8	1610
ARVCYGLGM	339	9	1611
CHQLCARGHCW	511	11	1612
CKKIFGSL	367	8	1613
CKKIFGSLAF	367	10	1614
CKKIFGSLAFL	367	11	1615
CRPRFREL	965	8	1616
CRVLQGLPREY	544	11	1617
CRWGLLLAL	7	9	1618
CRWGLLLALL	7	10	1619
DHVRENRGRL	808	10	1620
EKGERLPQPPI	936	11	1621
ERGAPPSTF	1229	9	1622
ERLPQPPI	939	8	1623
ERLPQPPICTI	939	11	1624
FHKNNQLAL	173	9	1625
FHKNNQLALTL	173	11	1626
FRELVSEF	969	8	1627
FRELVSEFSRM	969	11	1628
FRNPHQAL	486	8	1629
FRNPHQALL	486	9	1630
GKNGVVKDVF	1176	10	1631
GKVPIKWM	882	8	1632
GKVPIKWMAL	882	10	1633
GRILHNGAY	433	9	1634
GRILHNGAYSL	433	11	1635
GRLGSQDL	815	8	1636
GRLGSQDLL	815	9	1637
GRLGSQDLLNW	815	11	1638
HHNTHLCF	469	8	1639
HKNNQLAL	174	8	1640
HKNNQLALTL	174	10	1641
HKNNQLALTLI	174	11	1642
HRDLAARNVL	843	10	1643
HHHNTHLCF	468	9	1644
IKRRQQKI	675	8	1645
IKRRQQKIRKY	675	11	1646
IKWMALESI	886	9	1647
IKWMALESIL	886	10	1648
IRGRILHNGAY	431	11	1649
IRKYTMRRL	682	9	1650
IRKYTMRRLL	682	10	1651
KHSDCLACL	248	9	1652
KHSDCLACLHF	248	11	1653

Table XII
HER2/NEU B27 Supermotif Peptides

Sequence	Position	No. of Amino Acids	SEQ ID NO.
KKIFGSLAF	368	9	1654
KKIFGSLAFL	368	10	1655
KRRQQKIRKY	676	10	1656
LHCPALVTY	266	9	1657
LHFNHSGI	256	8	1658
LHFNHSGICEL	256	11	1659
LHNGAYSL	436	8	1660
LHNGAYSLTL	436	10	1661
LRELGSGL	458	8	1662
LRELGSGLAL	458	10	1663
LRELGSGLALI	458	11	1664
LRELQLRSL	137	9	1665
LRIVRGTQL	99	9	1666
LRIVRGTQLF	99	10	1667
LRLPASPETHL	33	11	1668
LRSLRELGSGL	455	11	1669
LRSLTEIL	142	8	1670
MRILKETEL	712	9	1671
MRRLLQETEL	687	10	1672
NHSGICEL	259	8	1673
NHVKITDF	857	8	1674
NHVKITDFGL	857	10	1675
NKEILDEAY	764	9	1676
NKEILDEAYVM	764	11	1677
NRGRLGSQDL	813	10	1678
NRGRLGSQDLL	813	11	1679
PHPPPAFSPAF	1207	11	1680
PKANKEIL	761	8	1681
PKHSDCLACL	247	10	1682
PREYVNARHCL	551	11	1683
PRFRELVSEF	967	10	1684
QKIRKYTM	680	8	1685
QKIRKYTMRRL	680	11	1686
QRASPLTSI	646	9	1687
QRASPLTSII	646	10	1688
QRFVVIQNEDL	984	11	1689
QRLRIVRGTQL	97	11	1690
QRNPQLCY	156	8	1691
QRYSEDPTVPL	1110	11	1692
RKVKVLGSGAF	721	11	1693
RKYTMRRL	683	8	1694
RKYTMRRLL	683	9	1695
RRFTHQSDVW	897	10	1696
RRLLQETEL	688	9	1697
RRQQKIRKY	677	9	1698
RRQQKIRKYTM	677	11	1699
RRRFTHQSDVW	896	11	1700
SKPCARVCY	335	9	1701
SKPCARVCYGL	335	11	1702
SRACHPCSPM	189	10	1703

Table XII
HER2/NEU B27 Supermotif Peptides

Sequence	Position	No. of Amino Acids	SEQ ID NO.
SRLLGICL	783	8	1704
SRMARDPQRF	977	10	1705
THDPSPLQRY	1103	10	1706
THLCFVHTVPW	472	11	1707
THLDMLRHL	41	9	1708
THLDMLRHLY	41	10	1709
THQSDVWSY	900	9	1710
TRSGGGDL	1052	8	1711
TRSGGGDLTL	1052	10	1712
VHRDLAARNVL	842	11	1713
VHTVPWDQL	477	9	1714
VHTVPWDQLF	477	10	1715
VKIPVAIKVL	746	10	1716
VKITDFGL	859	8	1717
VKITDFGLARL	859	11	1718
VKPDLSYM	604	8	1719
VKPDLSYMPI	604	10	1720
VKPDLSYMPIW	604	11	1721
VKSPNHVKI	853	9	1722
VKVLGSGAF	723	9	1723
VRAVTSANI	353	9	1724
VRENRGRL	810	8	1725
VRGTQLFEDNY	102	11	1726
VRLVHRDL	839	8	1727
VRQVPLQRL	91	9	1728
VRQVPLQRLRI	91	11	1729
WKDIFHKNNQL	169	11	1730
YHADGGKVPI	877	10	1731
YRSLLEDDDM	1005	10	1732

Table XIII
HER2/NEU B58 Supermotif Peptides

Sequence	Position	No. of Amino Acids	SEQ ID NO.
AAKGLQSL	1094	8	1733
AALCRWGL	4	8	1734
AALCRWGLL	4	9	1735
AALCRWGLLL	4	10	1736
AAPQPHPPPAF	1203	11	1737
AARPAGATL	1159	9	1738
ASCVTACPY	293	9	1739
ASCVTACPYNY	293	11	1740
ASLSFLQDI	69	9	1741
ASPETHLDM	37	9	1742
ASPETHLDML	37	10	1743
ASPGGLREL	132	9	1744
ASPGGLRELQL	132	11	1745
ASPLDSTF	997	8	1746
ASPLDSTFY	997	9	1747
ASPLTSII	648	8	1748
ASPLTSIISAV	648	11	1749
ASTQVCTGTDM	21	11	1750
ATLERPKTL	1165	9	1751
CAHYKDPPF	587	9	1752
CAHYKDPPFCV	587	11	1753
CARCKGPL	224	8	1754
CARVCYGL	338	8	1755
CARVCYGLGM	338	10	1756
CSKPCARV	334	8	1757
CSKPCARVCY	334	10	1758
CSPMCKGSRCW	195	11	1759
CSPQPEYV	1133	8	1760
CSQFLRGQECV	531	11	1761
CTGPKHSDCL	244	10	1762
CTGTDMKL	26	8	1763
CTGTDMKLRL	26	10	1764
CTHSCVDL	630	8	1765
CTIDVYMI	947	8	1766
CTIDVYMIM	947	9	1767
CTIDVYMIMV	947	10	1768
DSECRPRF	962	8	1769
DSECRPRFREL	962	11	1770
DSLPDLSV	417	8	1771
DSLPDLSVF	417	9	1772
DSTFYRSL	1001	8	1773
DSTFYRSLL	1001	9	1774
DTILWKDI	165	8	1775
DTILWKDIF	165	9	1776
EADQCVACAHY	580	11	1777
EAYVMAGV	770	8	1778
ESILRRRF	892	8	1779
ESMPNPEGRY	280	10	1780
ESSEDCQSL	207	9	1781
ETDGYVAPL	1123	9	1782

Table XIII
HER2/NEU B58 Supermotif Peptides

Sequence	Position	No. of Amino Acids	SEQ ID NO.
ETELRKVKV	717	9	1783
ETELRKVKVL	717	10	1784
ETELVEPL	693	8	1785
ETEYHADGGKV	874	11	1786
ETHLDMLRHL	40	10	1787
ETHLDMLRHLY	40	11	1788
ETLEEITGY	401	9	1789
ETLEEITGYL	401	10	1790
ETLEEITGYLY	401	11	1791
FAGCKKIF	364	8	1792
FAGCKKIFGSL	364	11	1793
FSPAFDNL	1213	8	1794
FSPAFDNLY	1213	9	1795
FSPAFDNLYY	1213	10	1796
FSPAFDNLYYW	1213	11	1797
FSRMARDPQRF	976	11	1798
FTHQSDVW	899	8	1799
FTHQSDVWSY	899	10	1800
GAAKGLQSL	1093	9	1801
GACQPCPI	621	8	1802
GAFGTVYKGI	729	10	1803
GAFGTVYKGIW	729	11	1804
GAGSDVFDGDL	1080	11	1805
GAKPYDGI	919	8	1806
GAMPNQAQM	704	9	1807
GAMPNQAQMRI	704	11	1808
GASCVTACPY	292	10	1809
GASPGGLREL	131	10	1810
GATLERPKTL	1164	10	1811
GAVENPEY	1189	8	1812
GAVENPEYL	1189	9	1813
GAYSLTLQGL	439	10	1814
GSCTLVCPL	309	9	1815
GSDVFDGDL	1082	9	1816
GSDVFDGDLGM	1082	11	1817
GSGAFGTV	727	8	1818
GSGAFGTVY	727	9	1819
GSLAFLPESF	372	10	1820
GSPYVSRL	778	8	1821
GSPYVSRLL	778	9	1822
GSPYVSRLLGI	778	11	1823
GSQDLLNW	818	8	1824
GSQDLLNWCM	818	10	1825
GTDMKLRL	28	8	1826
GTPTAENPEY	1239	10	1827
GTPTAENPEYL	1239	11	1828
GTQLFEDNY	104	9	1829
GTQLFEDNYAL	104	11	1830
GTVYKGIW	732	8	1831
GTVYKGIWI	732	9	1832

TableXIII
HER2/NEU B58 Supermotif Peptides

Sequence	Position	No. of Amino Acids	SEQ ID NO.
HADGGKVPI	878	9	1833
HADGGKVPIKW	878	11	1834
HSDCLACL	249	8	1835
HSDCLACLHF	249	10	1836
HTANRPEDECV	495	11	1837
HTVPWDQL	478	8	1838
HTVPWDQLF	478	9	1839
IAHNQVRQV	86	9	1840
IAHNQVRQVPL	86	11	1841
IAKGMSYL	829	8	1842
IAKGMSYLEDV	829	11	1843
ISAVVGIL	655	8	1844
ISAVVGILL	655	9	1845
ISAVVGILLV	655	10	1846
ISAVVGILLVV	655	11	1847
ISAWPDSL	412	8	1848
ISAWPDSLPDL	412	11	1849
ISWLGLRSL	450	9	1850
ITDFGLARL	861	9	1851
ITDFGLARLL	861	10	1852
ITGYLYISAW	406	10	1853
KANKEILDEAY	762	11	1854
KSPNHVKI	854	8	1855
KSPNHVKITDF	854	11	1856
KTLSPGKNGV	1171	10	1857
KTLSPGKNGVV	1171	11	1858
LAALCRWGL	3	9	1859
LAALCRWGLL	3	10	1860
LAALCRWGLLL	3	11	1861
LAARNVLV	846	8	1862
LACLHFNHSGI	253	11	1863
LAFLPESF	374	8	1864
LALHHHNTHL	465	10	1865
LAPSEGAGSDV	1075	11	1866
LAVLDNGDPL	114	10	1867
LSFLQDIQEV	71	10	1868
LSPGKNGV	1173	8	1869
LSPGKNGVV	1173	9	1870
LSTDVGSCTL	304	10	1871
LSTDVGSCTLV	304	11	1872
LSVFQNLQV	422	9	1873
LSVFQNLQVI	422	10	1874
LSYMPIWKF	608	9	1875
LTCSPQPEY	1131	9	1876
LTCSPQPEYV	1131	10	1877
LTEILKGGV	145	9	1878
LTEILKGGVL	145	10	1879
LTEILKGGVLI	145	11	1880
LTLQGLGI	443	8	1881
LTLQGLGISW	443	10	1882

Table XIII
HER2/NEU B58 Supermotif Peptides

Sequence	Position	No. of Amino Acids	SEQ ID NO.
LTLQGLGISWL	443	11	1883
LTSIISAV	651	8	1884
LTSIISAVV	651	9	1885
LTSIISAVVGI	651	11	1886
LTSTVQLV	790	8	1887
LTSTVQLVTQL	790	11	1888
LTYLPTNASL	62	10	1889
MAGVGSPY	774	8	1890
MAGVGSPYV	774	9	1891
MALESILRRRF	889	11	1892
MARDPQRF	979	8	1893
MARDPQRFV	979	9	1894
MARDPQRFVV	979	10	1895
MARDPQRFVVI	979	11	1896
MSYLEDVRL	833	9	1897
MSYLEDVRLV	833	10	1898
MTFGAKPY	916	8	1899
MTFGAKPYDGI	916	11	1900
NASLSFLQDI	68	10	1901
NTAPLQPEQL	388	10	1902
NTDTFESM	275	8	1903
NTHLCFVHTV	471	10	1904
NTSPKANKEI	758	10	1905
NTSPKANKEIL	758	11	1906
PAARPAGATL	1158	10	1907
PAEQRASPL	643	9	1908
PAFDNLYY	1215	8	1909
PAFDNLYYW	1215	9	1910
PAFSPAFDNL	1211	10	1911
PAFSPAFDNLY	1211	11	1912
PALVTYNTDTF	269	11	1913
PAPGAGGM	1035	8	1914
PAPGAGGMV	1035	9	1915
PAREIPDL	927	8	1916
PAREIPDLL	927	9	1917
PASNTAPL	385	8	1918
PASPETHL	36	8	1919
PASPETHLDM	36	10	1920
PASPETHLDML	36	11	1921
PASPLDSTF	996	9	1922
PASPLDSTFY	996	10	1923
PSEEEAPRSPL	1065	11	1924
PSEGAGSDV	1077	9	1925
PSEGAGSDVF	1077	10	1926
PSETDGYV	1121	8	1927
PSETDGYVAPL	1121	11	1928
PSGAMPNQAQM	702	11	1929
PSGVKPDL	601	8	1930
PSGVKPDLSY	601	10	1931
PSGVKPDLSYM	601	11	1932

Table XIII
HER2/NEU B58 Supermotif Peptides

Sequence	Position	No. of Amino Acids	SEQ ID NO.
PSPREGPL	1150	8	1933
PTAENPEY	1241	8	1934
PTAENPEYL	1241	9	1935
PTAENPEYLGL	1241	11	1936
PTHDPSPL	1102	8	1937
PTHDPSPLQRY	1102	11	1938
PTNASLSF	66	8	1939
PTNASLSFL	66	9	1940
PTQCVNCSQF	525	10	1941
PTQCVNCSQFL	525	11	1942
QSDVWSYGV	902	9	1943
QSDVWSYGVTV	902	11	1944
QSLPTHDPSPL	1099	11	1945
RACHPCSPM	190	9	1946
RASPLTSI	647	8	1947
RASPLTSII	647	9	1948
RAVTSANI	354	8	1949
RAVTSANIQEF	354	11	1950
RSGGGDLTL	1053	9	1951
RSGGGDLTLGL	1053	11	1952
RSLLEDDDM	1006	9	1953
RSLRELGSGL	456	10	1954
RSLTEILKGGV	143	11	1955
RSRACHPCSPM	188	11	1956
SAVVGILL	656	8	1957
SAVVGILLV	656	9	1958
SAVVGILLVV	656	10	1959
SAVVGILLVVV	656	11	1960
SAWPDSLPDL	413	10	1961
SSEDCQSL	208	8	1962
SSSTRSGGGDL	1049	11	1963
SSTRSGGGDL	1050	10	1964
STDVGSCTL	305	9	1965
STDVGSCTLV	305	10	1966
STFYRSLL	1002	8	1967
STQVCIGTDM	22	10	1968
STRSGGGDL	1051	9	1969
STRSGGGDLTL	1051	11	1970
STVQLVTQL	792	9	1971
STVQLVTQLM	792	10	1972
TACPYNYL	297	8	1973
TAENPEYL	1242	8	1974
TAENPEYLGL	1242	10	1975
TANRPEDECV	496	10	1976
TAPLQPEQL	389	9	1977
TAPLQPEQLQV	389	11	1978
TSANIQEF	357	8	1979
TSIISAVV	652	8	1980
TSIISAVVGI	652	10	1981
TSIISAVVGIL	652	11	1982

Table XIII

HER2/NEU B58 Supermotif Peptides

Sequence	Position	No. of Amino Acids	SEQ ID NO.
TSPKANKEI	759	9	1983
TSPKANKEIL	759	10	1984
TSTVQLVTQL	791	10	1985
TSTVQLVTQLM	791	11	1986
VACAHYKDPPF	585	11	1987
VARCPSGV	597	8	1988
VSRLLGICL	782	9	1989
VTACPYNY	296	8	1990
VTACPYNYL	296	9	1991
VTGASPGGL	129	9	1992
VTQLMPYGCL	797	10	1993
VTQLMPYGCLL	797	11	1994
VTSANIQEF	356	9	1995
VTVWELMTF	910	9	1996
VTYNTDTF	272	8	1997
VTYNTDTFESM	272	11	1998
WSYGVTVW	906	8	1999
WSYGVTVWEL	906	10	2000
WSYGVTVWELM	906	11	2001
YSEDPTVPL	1112	9	2002
YSLTLQGL	441	8	2003
YSLTLQGLGI	441	10	2004
YTFGASCV	289	8	2005

Table XIV
HER2/NEU B62 Supermotif Peptides

Sequence	Position	No. of Amino Acids	SEQ ID NO.
ALESILRRRF	890	10	2006
ALHHHNTHLCF	466	11	2007
ALVTYNTDTF	270	10	2008
AMPNQAQM	705	8	2009
AMPNQAQMRI	705	10	2010
APGAGGMV	1036	8	2011
APLQPEQLQV	390	10	2012
APLQPEQLQVF	390	11	2013
APLTCSPQPEY	1129	11	2014
APQPHPPPAF	1204	10	2015
APSEGAGSDV	1076	10	2016
APSEGAGSDVF	1076	11	2017
AVTSANIQEF	355	10	2018
AVVGILLV	657	8	2019
AVVGILLVV	657	9	2020
AVVGILLVVV	657	10	2021
CLHFNHSGI	255	9	2022
CLTSTVQLV	789	9	2023
CMQIAKGM	826	8	2024
CMQIAKGMSY	826	10	2025
CPDPAPGAGGM	1032	11	2026
CPINCTHSCV	626	10	2027
CPLHNQEV	315	8	2028
CPSGVKPDLSY	600	11	2029
CPYNYLSTDV	299	10	2030
CQPQNGSV	567	8	2031
CQPQNGSVTCF	567	11	2032
CQSLTRTV	212	8	2033
CVARCPSGV	596	9	2034
CVTACPYNY	295	9	2035
DIQEVQGY	76	8	2036
DIQEVQGYV	76	9	2037
DIQEVQGYVLI	76	11	2038
DLAARNVLV	845	9	2039
DLLNWCMQI	821	9	2040
DLSVFQNLQV	421	10	2041
DLSVFQNLQVI	421	11	2042
DLSYMPIW	607	8	2043
DLSYMPIWKF	607	10	2044
DLVDAEEY	1016	8	2045
DLVDAEEYLV	1016	10	2046
DMGDLVDAEEY	1013	11	2047
DPAPGAGGM	1034	9	2048
DPAPGAGGMV	1034	10	2049
DPLNNTTPV	121	9	2050
DPQRFVVI	982	8	2051
DPSPLQRY	1105	8	2052
DQCVACAHY	582	9	2053
DVFAFGGAV	1183	9	2054
DVFDGDLGM	1084	9	2055

Table XIV
HER2/NEU B62 Supermotif Peptides

Sequence	Position	No. of Amino Acids	SEQ ID NO.
DVGSCTLV	307	8	2056
DVWSYGVTV	904	9	2057
DVWSYGVTVW	904	10	2058
DVYMIMVKCW	950	10	2059
DVYMIMVKCWM	950	11	2060
EILDEAYV	766	8	2061
EILDEAYVM	766	9	2062
EILKGGVLI	147	9	2063
EITGYLYI	405	8	2064
EITGYLYISAW	405	11	2065
ELAALCRW	2	8	2066
ELGSGLALI	460	9	2067
ELHCPALV	265	8	2068
ELHCPALVTY	265	10	2069
ELMTFGAKPY	914	10	2070
ELQLRSLTEI	139	10	2071
ELVSEFSRM	971	9	2072
EPLTPSGAM	698	9	2073
EQRASPLTSI	645	10	2074
EQRASPLTSII	645	11	2075
EVQGYVLI	79	8	2076
EVRAVTSANI	352	10	2077
FLQDIQEV	73	8	2078
FLQDIQEVQGY	73	11	2079
FLRGQECV	534	8	2080
FQNLQVIRGRI	425	11	2081
FVHTVPWDQLF	476	11	2082
GICELHCPALV	262	11	2083
GICLTSTV	787	8	2084
GICLTSTVQLV	787	11	2085
GILIKRRQQKI	672	11	2086
GILLVVVLGV	660	10	2087
GILLVVVLGVV	660	11	2088
GIWIPDGENV	737	10	2089
GLARLLDI	865	8	2090
GLGMEHLREV	344	10	2091
GMEHLREV	346	8	2092
GMEHLREVRAV	346	11	2093
GMSYLEDV	832	8	2094
GMSYLEDVRLV	832	11	2095
GPASPLDSTF	995	10	2096
GPASPLDSTFY	995	11	2097
GPEADQCV	578	8	2098
GPGPTQCV	522	8	2099
GPTQCVNCSQF	524	11	2100
GQECVEECRV	537	10	2101
GVKPDLSY	603	8	2102
GVKPDLSYM	603	9	2103
GVKPDLSYMPI	603	11	2104
GVTVWELM	909	8	2105

Table XIV
HER2/NEU B62 Supermotif Peptides

Sequence	Position	No. of Amino Acids	SEQ ID NO.
GVTVWELMTF	909	10	2106
GVVFGILI	668	8	2107
GVVKDVFAF	1179	9	2108
HLCFVHTV	473	8	2109
HLCFVHTVPW	473	10	2110
HLDMLRHLY	42	9	2111
HLREVRAV	349	8	2112
HLYQGCQV	48	8	2113
HLYQGCQVV	48	9	2114
HPECQPQNGSV	564	11	2115
HPPPAFSPAF	1208	10	2116
HQLCARGHCW	512	10	2117
HQSDVWSY	901	8	2118
HQSDVWSYGV	901	10	2119
HSAVVGI	654	8	2120
HSAVVGILLV	654	11	2121
ILDEAYVM	767	8	2122
ILDEAYVMAGV	767	11	2123
ILIKRRQQKI	673	10	2124
ILKETELRKV	714	10	2125
ILKGGVLI	148	8	2126
ILLVVVLGV	661	9	2127
ILLVVVLGVV	661	10	2128
ILLVVVLGVVF	661	11	2129
IMVKCWMI	954	8	2130
IPDGENVKI	740	9	2131
IPDGENVKIPV	740	11	2132
IQEFAGCKKI	361	10	2133
IQEFAGCKKIF	361	11	2134
IQEVQGYV	77	8	2135
IQEVQGYVLI	77	10	2136
IQRNPQLCY	155	9	2137
IVRGTQLF	101	8	2138
KIFGSLAF	369	8	2139
KIPVAIKV	747	8	2140
KPCARVCY	336	8	2141
KPDLSYMPI	605	9	2142
KPDLSYMPIW	605	10	2143
KPYDGIPAREI	921	11	2144
KVKVLGSGAF	722	10	2145
KVLGSGAF	724	8	2146
KVLGSGAFGTV	724	11	2147
LIAHNQVRQV	85	10	2148
LIHHNTHLCF	467	10	2149
LIHHNTHLCFV	467	11	2150
LIKRRQQKI	674	9	2151
LIQRNPQLCY	154	10	2152
LLDIDETEY	869	9	2153
LLEDDDMGDLV	1008	11	2154
LLGICLTSTV	785	10	2155

Table XIV
HER2/NEU B62 Supermotif Peptides

Sequence	Position	No. of Amino Acids	SEQ ID NO.
LLNWCMQI	822	8	2156
LLPPGAASTQV	15	11	2157
LLQETELV	690	8	2158
LLVVVLGV	662	8	2159
LLVVVLGVV	662	9	2160
LLVVVLGVVF	662	10	2161
LMPYGCLLDHV	800	11	2162
LMTFGAKPY	915	9	2163
LPASPETHLDM	35	11	2164
LPPGAASTQV	16	10	2165
LPQPPICTI	941	9	2166
LPQPPICTIDV	941	11	2167
LPSETDGY	1120	8	2168
LPSETDGYV	1120	9	2169
LPTNASLSF	65	9	2170
LQDIQEVQGY	74	10	2171
LQDIQEVQGYV	74	11	2172
LQGLGISW	445	8	2173
LQGLPREY	547	8	2174
LQGLPREYV	547	9	2175
LQLRSLTEI	140	9	2176
LQPEQLQV	392	8	2177
LQPEQLQVF	392	9	2178
LQRYSEDPTV	1109	10	2179
LQVFETLEEI	397	10	2180
LQVIRGRI	428	8	2181
LVCPLHNQEV	313	10	2182
LVDAEEYLV	1017	9	2183
LVEPLTPSGAM	696	11	2184
LVHRDLAARNV	841	11	2185
LVKSPNHV	852	8	2186
LVKSPNHVKI	852	10	2187
LVPQQGFF	1024	8	2188
LVSEFSRM	972	8	2189
LVTQLMPY	796	8	2190
LVTYNTDTF	271	9	2191
LVVVLGVV	663	8	2192
LVVVLGVVF	663	9	2193
LVVVLGVVFGI	663	11	2194
MIDSECRPRF	960	10	2195
MIMVKCWM	953	8	2196
MIMVKCWMI	953	9	2197
MLRHLYQGCQV	45	11	2198
MPNPEGRY	282	8	2199
MPNPEGRYTF	282	10	2200
MPNQAQMRI	706	9	2201
MPYGCLLDHV	801	10	2202
MQIAKGMSY	827	9	2203
NIQEFAGCKKI	360	11	2204
NLQVIRGRI	427	9	2205

Table XIV
HER2/NEU B62 Supermotif Peptides

Sequence	Position	No. of Amino Acids	SEQ ID NO.
NPEGRYTF	284	8	2206
NPEYLGLDV	1245	9	2207
NPEYLGLDVPV	1245	11	2208
NPQLCYQDTI	158	10	2209
NQLALTLI	177	8	2210
NVKIPVAI	745	8	2211
NVKIPVAIKV	745	10	2212
NVLVKSPNHV	850	10	2213
PICTIDVY	945	8	2214
PICTIDVYM	945	9	2215
PICTIDVYMI	945	10	2216
PICTIDVYMIM	945	11	2217
PIKWMALESI	885	10	2218
PINCTHSCV	627	9	2219
PLNNTTPV	122	8	2220
PLPSETDGY	1119	9	2221
PLPSETDGYV	1119	10	2222
PLQPEQLQV	391	9	2223
PLQPEQLQVF	391	10	2224
PLQRLRIV	95	8	2225
PLQRYSEDPTV	1108	11	2226
PLTCSPQPEY	1130	10	2227
PLTCSPQPEYV	1130	11	2228
PLTPSGAM	699	8	2229
PLTSIISAV	650	9	2230
PLTSIISAVV	650	10	2231
PMCKGSRCW	197	9	2232
PPAFSPAF	1210	8	2233
PPERGAPPSTF	1227	11	2234
PPGAASTQV	17	9	2235
PPICTIDV	944	8	2236
PPICTIDVY	944	9	2237
PPICTIDVYM	944	10	2238
PPICTIDVYMI	944	11	2239
PPPAFSPAF	1209	9	2240
PQLCYQDTI	159	9	2241
PQLCYQDTILW	159	11	2242
PQNGSVTCF	569	9	2243
PQPEYVNQPDV	1135	11	2244
PQPHPPPAF	1205	9	2245
PQPPICTI	942	8	2246
PQPPICTIDV	942	10	2247
PQPPICTIDVY	942	11	2248
QIAKGMSY	828	8	2249
QLCARGHCW	513	9	2250
QLCYQDTI	160	8	2251
QLCYQDTILW	160	10	2252
QLFEDNYALAV	106	11	2253
QLQVFETLEEI	396	11	2254
QLRSLTEI	141	8	2255

Table XIV
HER2/NEU B62 Supermotif Peptides

Sequence	Position	No. of Amino Acids	SEQ ID NO.
QLVTQLMPY	795	9	2256
QPEQLQVF	393	8	2257
QPEYVNQPDV	1136	10	2258
QPHPPPAF	1206	8	2259
QPPICTIDV	943	9	2260
QPPICTIDVY	943	10	2261
QPPICTIDVYM	943	11	2262
QPQNGSVTCF	568	10	2263
QQKIRKYTM	679	9	2264
QVCTGTDM	24	8	2265
QVFETLEEI	398	9	2266
QVPLQRLRI	93	9	2267
QVPLQRLRIV	93	10	2268
QVVQGNLELTY	54	11	2269
RILHNGAY	434	8	2270
RILKETELRKV	713	11	2271
RIVRGTQLF	100	9	2272
RLGSQDLLNW	816	10	2273
RLLDIDETEY	868	10	2274
RLLGICLTSTV	784	11	2275
RLLQETELV	689	9	2276
RLPQPPICTI	940	10	2277
RLRIVRGTQLF	98	11	2278
RMARDPQRF	978	9	2279
RMARDPQRFV	978	10	2280
RMARDPQRFVV	978	11	2281
RPRFRELV	966	8	2282
RPRFRELVSEF	966	11	2283
RQQKIRKY	678	8	2284
RQQKIRKYTM	678	10	2285
RQVPLQRLRI	92	10	2286
RQVPLQRLRIV	92	11	2287
RVCYGLGM	340	8	2288
RVLQGLPREY	545	10	2289
RVLQGLPREYV	545	11	2290
SIISAVVGI	653	9	2291
SLAFLPESF	373	9	2292
SLLEDDDM	1007	8	2293
SLPDLSVF	418	8	2294
SLSFLQDI	70	8	2295
SLSFLQDIQEV	70	11	2296
SLTEILKGGV	144	10	2297
SLTLQGLGI	442	9	2298
SLTLQGLGISW	442	11	2299
SMPNPEGRY	281	9	2300
SMPNPEGRYTF	281	11	2301
SPAFDNLY	1214	8	2302
SPAFDNLYY	1214	9	2303
SPAFDNLYYW	1214	10	2304
SPETHLDM	38	8	2305

Table XIV
HER2/NEU B62 Supermotif Peptides

Sequence	Position	No. of Amino Acids	SEQ ID NO.
SPGKNGVV	1174	8	2306
SPGKNGVVKDV	1174	11	2307
SPKANKEI	760	8	2308
SPLDSTFY	998	8	2309
SPLTSHSAV	649	10	2310
SPLTSHSAVV	649	11	2311
SPMCKGSRCW	196	10	2312
SPNHVKITDF	855	10	2313
SPYVSRLLGI	779	10	2314
SQDLLNWCM	819	9	2315
SQDLLNWCMQI	819	11	2316
SQFLRGQECV	532	10	2317
SVFQNLQV	423	8	2318
SVFQNLQVI	423	9	2319
TIDVYMIM	948	8	2320
TIDVYMIMV	948	9	2321
TILWKDIF	166	8	2322
TLEEITGY	402	8	2323
TLEEITGYLY	402	10	2324
TLEEITGYLYI	402	11	2325
TLQGLGISW	444	9	2326
TLSPGKNGV	1172	9	2327
TLSPGKNGVV	1172	10	2328
TLVCPLHNQEV	312	11	2329
TPTAENPEY	1240	9	2330
TQCVNCSQF	526	9	2331
TQLFEDNY	105	8	2332
TQVCTGTDM	23	9	2333
TVPLPSETDGY	1117	11	2334
TVPWDQLF	479	8	2335
TVQLVTQLM	793	9	2336
TVQLVTQLMPY	793	11	2337
TVWELMTF	911	8	2338
TVYKGIWI	733	8	2339
VLGSGAFGTV	725	10	2340
VLGSGAFGTVY	725	11	2341
VLGVVFGI	666	8	2342
VLGVVFGILI	666	10	2343
VLIAHNQV	84	8	2344
VLIAHNQVRQV	84	11	2345
VLIQRNPQLCY	153	11	2346
VLQGLPREY	546	9	2347
VLQGLPREYV	546	10	2348
VLVKSPNHV	851	9	2349
VLVKSPNHVKI	851	11	2350
VMAGVGSPY	773	9	2351
VMAGVGSPYV	773	10	2352
VPIKWMALESI	884	11	2353
VPLPSETDGY	1118	10	2354
VPLPSETDGYV	1118	11	2355

Table XV

HER2/NEU B62 Supermotif Peptides

Sequence	Position	No. of Amino Acids	SEQ ID NO.
VPLQRLRI	94	8	2356
VPLQRLRIV	94	9	2357
VQGNLELTY	56	9	2358
VQLVTQLM	794	8	2359
VQLVTQLMPY	794	10	2360
VVGILLVV	658	8	2361
VVGILLVVV	658	9	2362
VVKDVFAF	1180	8	2363
VVLGVVFGI	665	9	2364
VVLGVVFGILI	665	11	2365
VVQGNLELTY	55	10	2366
VVVLGVVF	664	8	2367
VVVLGVVFGI	664	10	2368
WIPDGENV	739	8	2369
WIPDGENVKI	739	10	2370
WMIDSECRPRF	959	11	2371
WPDSLPDLSV	415	10	2372
WPDSLPDLSVF	415	11	2373
YLEDVRLV	835	8	2374
YLGLDVPV	1248	8	2375
YLPTNASLSF	64	10	2376
YLVPQQGF	1023	8	2377
YLVPQQGFF	1023	9	2378
YMIMVKCW	952	8	2379
YMIMVKCWM	952	9	2380
YMIMVKCWMI	952	10	2381
YQDTILWKDI	163	10	2382
YQDTILWKDIF	163	11	2383
YVLIAHNQV	83	9	2384
YVMAGVGSPY	772	10	2385
YVMAGVGSPYV	772	11	2386
YVSRLLGI	781	8	2387

Table XV
HER2/NEU A01 Motif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*0101	SEQ ID NO.
AFSPAFDNLY	1212	10	0 0010	2388
AFSPAFDNLYY	1212	11	0.0140	2389
ASCVTACPY	293	9	0.0550	2390
ASCVTACPYNY	293	11	0.1900	2391
ASPLDSTFY	997	9	0.0290	2392
CMQIAKGMSY	826	10	0.3000	2393
CPSGVKPDLSY	600	11		2394
CSKPCARVCY	334	10	0.0016	2395
DMGDLVDAEEY	1013	11	0 0027	2396
DPSPLQRY	1105	8		2397
EADQCVACAHY	580	11	0 1000	2398
ESMPNPEGRY	280	10	0 1800	2399
ETHLDMLRHLY	40	11	0.2800	2400
ETLEEITGY	401	9	0 0430	2401
ETLEEITGYLY	401	11	0.4400	2402
FESMPNPEGRY	279	11	0.0049	2403
FGASCVTACPY	291	11	0 0100	2404
FSPAFDNLY	1213	9	0.0430	2405
FSPAFDNLYY	1213	10	5 5000	2406
FTHQSDVWSY	899	10	2.7000	2407
GASCVTACPY	292	10	0 0012	2408
GGAVENPEY	1188	9		2409
GPASPLDSTFY	995	11		2410
GSGAFGTVY	727	9	0.0011	2411
GTPTAENPEY	1239	10	0.0630	2412
GTQLFEDNY	104	9	0.1800	2413
HLDMLRHLY	42	9	9 1000	2414
HQSDVWSY	901	8	-0.0021	2415
KCSKPCARVCY	333	11	-0 0017	2416
LEEITGYLY	403	9	0.0057	2417
LGSGAFGTVY	726	10	0.0010	2418
LLDIDETEY	869	9	7.6000	2419
LMTFGAKPY	915	9	0.0011	2420
LPSETDGY	1120	8		2421
LQDIQEVQGY	74	10	0 0015	2422
LTCSPQPEY	1131	9	0.1300	2423
MGDLVDAEEY	1014	10	0 0120	2424
MTFGAKPY	916	8	-0 0021	2425
NKEILDEAY	764	9	0.0017	2426
PASPLDSTFY	996	10	0.0150	2427
PSGVKPDLSY	601	10	0.0010	2428
PTAENPEY	1241	8	0.0030	2429
PTHDPSPLQRY	1102	11	0.0160	2430
QIAKGMSY	828	8	-0.0021	2431
SGAFGTVY	728	8	-0.0021	2432
SMPNPEGRY	281	9	0.0028	2433
SPAFDNLY	1214	8		2434
SPAFDNLYY	1214	9		2435
TCSPQPEY	1132	8	-0 0021	2436
THDPSPLQRY	1103	10	0.0015	2437

Table XV
HER2/NEU A01 Motif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*0101	SEQ ID NO.
TLEEITGY	402	8	-0.0021	2438
TLEEITGYLY	402	10	1.1000	2439
VFETLEEITGY	399	11	0.0045	2440
VMAGVGSPY	773	9	0.0400	2441
VTACPYNY	296	8	0 1000	2442

Table XVI
HER2/NEU A03 Motif Peptides with Binding Data

Sequence	Position	No of Amino Acids	A*0301	SEQ ID NO.
AAGCTGPK	241	8		2443
AAGCTGPKH	241	9		2444
AAKGLQSLPTH	1094	11		2445
AALCRWGLLLA	4	11		2446
AAPQPHPPPA	1203	10		2447
AAPQPHPPPAF	1203	11		2448
AARNVLVK	847	8		2449
AARPAGATLER	1159	11		2450
ACAHYKDPPF	586	10		2451
ACHPCSPMCK	191	10		2452
ACHQLCAR	510	8		2453
ACHQLCARGH	510	10		2454
ACQPCPINCTH	622	11		2455
ADGGKVPIK	879	9		2456
ADQCVACA	581	8		2457
ADQCVACAH	581	9		2458
ADQCVACAHY	581	10		2459
ADQCVACAHYK	581	11		2460
AFGGAVENPEY	1186	11		2461
AFSPAFDNLY	1212	10	0.0003	2462
AFSPAFDNLYY	1212	11		2463
AGATLERPK	1163	9		2464
AGCKKIFGSLA	365	11		2465
AGCTGPKH	242	8		2466
AGGCARCK	221	8		2467
AGGMVHHR	1039	8		2468
AGGMVHHRH	1039	9		2469
AGGMVHHRHR	1039	10		2470
AGVGSPYVSR	775	10		2471
ALCRWGLLLA	5	10		2472
ALESILRR	890	8		2473
ALESILRRR	890	9	0.0013	2474
ALESILRRRF	890	10		2475
ALHHHNTH	466	8		2476
ALHHHNTHLCF	466	11		2477
ALLHTANR	492	8		2478
ALLPPGAA	14	8		2479
ALTLIDTNR	180	9	0.0004	2480
ALTLIDTNRSR	180	11		2481
ALVTYNTDTF	270	10		2482
AMPNQAQMR	705	9	0 0004	2483
ASCVTACPY	293	9	0.0008	2484
ASCVTACPYNY	293	11		2485
ASPETHLDMLR	37	11		2486
ASPLDSTF	997	8		2487
ASPLDSTFY	997	9	0.0002	2488
ASPLDSTFYR	997	10	0.0003	2489
ASPLTSHSA	648	10		2490
AVTSANIQEF	355	10		2491
AVTSANIQEFA	355	11		2492

Table XVI
HER2/NEU A03 Motif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*0301	SEQ ID NO.
CAAGCTGPK	240	9	0.0021	2493
CAAGCTGPKH	240	10		2494
CAGGCARCK	220	9	-0.0002	2495
CAHYKDPPF	587	9		2496
CCHEQCAA	235	8		2497
CFGPEADQCVA	576	11		2498
CLACLHFNH	252	9		2499
CLLDHVRENR	805	10	0.0003	2500
CMQIAKGMSY	826	10	0.0003	2501
CSKPCARVCY	334	10	0.0003	2502
CSPMCKGSR	195	9	-0.0008	2503
CTGPKHSDCLA	244	11		2504
CTGTDMKLR	26	9	0.0002	2505
CTHSCVDLDDK	630	11		2506
CTIDVYMIMVK	947	11		2507
CTLVCPLH	311	8		2508
CVACAHYK	584	8		2509
CVARCPSGVK	596	10	0.0220	2510
CVDLDDKGCPA	634	11		2511
CVGEGLACH	504	9		2512
CVNCSQFLR	528	9	0.0015	2513
CVTACPYNY	295	9	0.0002	2514
DCCHEQCA	234	8		2515
DCCHEQCAA	234	9		2516
DCLACLHF	251	8		2517
DCLACLHFNH	251	10		2518
DCQSLTRTVCA	211	11		2519
DDDMGDLVDA	1011	10		2520
DDKGCPAEQR	638	10		2521
DDKGCPAEQRA	638	11		2522
DDMGDLVDA	1012	9		2523
DGDLGMGA	1087	8		2524
DGDLGMGAA	1087	9		2525
DGDLGMGAAK	1087	10		2526
DGDPASNTA	382	9		2527
DGENVKIPVA	742	10		2528
DGGKVPIK	880	8		2529
DGGKVPIKWMA	880	11		2530
DGTQRCEK	326	8		2531
DGTQRCEKCSK	326	11		2532
DIDETEYH	871	8		2533
DIDETEYHA	871	9		2534
DIFHKNNQLA	171	10		2535
DIQEVQGY	76	8		2536
DLAARNVLVK	845	10	0.0018	2537
DLDDKGCPA	636	9		2538
DLGMGAAK	1089	8		2539
DLLEKGER	933	8		2540
DLLNWCMQIA	821	10		2541
DLLNWCMQIAK	821	11		2542

Table XVI
HER2/NEU A03 Motif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*0301	SEQ ID NO.
DLSYMPIWK	607	9	0 0005	2543
DLSYMPIWKF	607	10		2544
DLVDAEEY	1016	8		2545
DMGDLVDA	1013	8		2546
DMGDLVDAEEY	1013	11		2547
DMKLRLPA	30	8		2548
DSECRPRF	962	8		2549
DSECRPRFR	962	9	-0.0002	2550
DSLPDLSVF	417	9		2551
DTILWKDIF	165	9		2552
DTILWKDIFH	165	10		2553
DTILWKDIFHK	165	11		2554
DTNRSRACH	185	9		2555
DVFAFGGA	1183	8		2556
DVFDGDLGMGA	1084	11		2557
DVRLVHRDLA	838	10		2558
DVRLVHRDLAA	838	11		2559
DVRPQPPSPR	1144	10	0.0003	2560
DVYMIMVK	950	8		2561
EADQCVACA	580	9		2562
EADQCVACAH	580	10		2563
EADQCVACAHY	580	11		2564
EAPRSPLA	1069	8		2565
ECRVLQGLPR	543	10		2566
ECVGEGLA	503	8		2567
ECVGEGLACH	503	10		2568
EDCQSLTR	210	8		2569
EDDDMGDLVDA	1010	11		2570
EDECVGEGLA	501	10		2571
EDGTQRCEK	325	9		2572
EDVRLVHR	837	8		2573
EDVRLVHRDLA	837	11		2574
EFAGCKKIF	363	9		2575
EFSRMARDPQR	975	11		2576
EGAGSDVF	1079	8		2577
EGLACHQLCA	507	10		2578
EGLACHQLCAR	507	11		2579
EGPLPAAR	1154	8		2580
EGPLPAARPA	1154	10		2581
EGRYTFGA	286	8		2582
EILDEAYVMA	766	10		2583
EILKGGVLIQR	147	11		2584
EIPDLLEK	930	8		2585
EIPDLLEKGER	930	11		2586
EITGYLYISA	405	10		2587
ELGSGLALIH	460	10		2588
ELGSGLALIHH	460	11		2589
ELHCPALVTY	265	10	0.0002	2590
ELMTFGAK	914	8		2591
ELMTFGAKPY	914	10	0.0002	2592

Table XVI

HER2/NEU A03 Motif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*0301	SEQ ID NO.
ELTYLPTNA	61	9		2593
ELVEPLTPSGA	695	11		2594
ELVSEFSR	971	8		2595
ELVSEFSRMA	971	10		2596
ELVSEFSRMAR	971	11		2597
ESFDGDPA	379	8		2598
ESILRRRF	892	8		2599
ESILRRRFTH	892	10		2600
ESMPNPEGR	280	9	0.0003	2601
ESMPNPEGRY	280	10	0.0003	2602
ESSEDCQSLTR	207	11		2603
ETELRKVK	717	8		2604
ETEYHADGGK	874	10	0.0003	2605
ETHLDMLR	40	8		2606
ETHLDMLRH	40	9		2607
ETHLDMLRHLY	40	11		2608
ETLEEITGY	401	9	0.0002	2609
ETLEEITGYLY	401	11		2610
EVQGYVLIA	79	9		2611
EVQGYVLIAH	79	10		2612
EVRAVTSA	352	8		2613
EVTAEDGTQR	321	10	0.0002	2614
FAGCKKIF	364	8		2615
FCPDPAPGA	1031	9		2616
FCVARCPSGVK	595	11		2617
FDGDLGMGA	1086	9		2618
FDGDLGMGAA	1086	10		2619
FDGDLGMGAAK	1086	11		2620
FDGDPASNTA	381	10		2621
FFCPDPAPGA	1030	10		2622
FGAKPYDGIPA	918	11		2623
FGASCVTA	291	8		2624
FGASCVTACPY	291	11		2625
FGGAVENPEY	1187	10		2626
FGILIKRR	671	8		2627
FGILIKRRQQK	671	11		2628
FGPEADQCVA	577	10		2629
FGSLAFLPESF	371	11		2630
FLPESFDGDPA	376	11		2631
FLQDIQEVQGY	73	11		2632
FSPAFDNLY	1213	9	0.0002	2633
FSPAFDNLYY	1213	10	0.0005	2634
FSRMARDPQR	976	10	-0.0002	2635
FSRMARDPQRF	976	11		2636
FTHQSDVWSY	899	10	0.0003	2637
FVHTVPWDQLF	476	11		2638
GAAPQPHPPPA	1202	11		2639
GAFGTVYK	729	8		2640
GAGGMVHH	1038	8		2641
GAGGMVHHR	1038	9	-0 0002	2642

Table XVI
HER2/NEU A03 Motif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*0301	SEQ ID NO.
GAGGMVHHRH	1038	10		2643
GAGGMVHHRHR	1038	11		2644
GAKPYDGIPA	919	10		2645
GAKPYDGIPAR	919	11		2646
GAMPNQAQMR	704	10	-0.0002	2647
GAPPSTFK	1231	8		2648
GASCVTACPY	292	10	0.0003	2649
GASPGGLR	131	8		2650
GATLERPK	1164	8		2651
GAVENPEY	1189	8		2652
GCKKIFGSLA	366	10		2653
GCKKIFGSLAF	366	11		2654
GCLLDHVR	804	8		2655
GCLLDHVRENR	804	11		2656
GCPAEQRA	641	8		2657
GDLGMGAA	1088	8		2658
GDLGMGAAK	1088	9		2659
GDLVDAEEY	1015	9		2660
GDPASNTA	383	8		2661
GFFCPDPA	1029	8		2662
GFFCPDPAPGA	1029	11		2663
GGAAPQPH	1201	8		2664
GGAVENPEY	1188	9	0.0003	2665
GGKVPIKWMA	881	10		2666
GGLRELQLR	135	9		2667
GGMVHHRH	1040	8		2668
GGMVHHRHR	1040	9		2669
GICELHCPA	262	9		2670
GILIKRRQQK	672	10	0.0150	2671
GISWLGLR	449	8		2672
GISWLGLRSLR	449	11		2673
GIWIPDGENVK	737	11		2674
GLACHQLCA	508	9		2675
GLACHQLCAR	508	10	0.0110	2676
GLALHHHNTH	464	10		2677
GLEPSEEEA	1062	9		2678
GLEPSEEEAPR	1062	11		2679
GLGISWLGLR	447	10	0.0037	2680
GLGMEHLR	344	8		2681
GLGMEHLREVR	344	11		2682
GLLLALLPPGA	10	11		2683
GLPREYVNA	549	9		2684
GLPREYVNAR	549	10	0.0002	2685
GLPREYVNARH	549	11		2686
GLQSLPTH	1097	8		2687
GLRELQLR	136	8		2688
GMEHLREVR	346	9	-0.0002	2689
GMEHLREVRA	346	10		2690
GMSYLEDVR	832	9	-0.0002	2691
GMVHHRHR	1041	8		2692

Table XVI
HER2/NEU A03 Motif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*0301	SEQ ID NO.
GSCTLVCPLH	309	10		2693
GSGAFGTVY	727	9	0.0028	2694
GSGAFGTVYK	727	10	0.0660	2695
GSGLALIH	462	8		2696
GSGLALIHH	462	9		2697
GSLAFLPESF	372	10		2698
GSVTCFGPEA	572	10		2699
GTDMKLRLPA	28	10		2700
GTPTAENPEY	1239	10	0.0002	2701
GTQLFEDNY	104	9	0 0001	2702
GTQLFEDNYA	104	10		2703
GTQRCEKCSK	327	10	0.0210	2704
GVGSPYVSR	776	9	0.0010	2705
GVKPDLSY	603	8		2706
GVTVWELMTF	909	10		2707
GVVFGILIK	668	9	0.0047	2708
GVVFGILIKR	668	10	0.0180	2709
GVVFGILIKRR	668	11		2710
GVVKDVFA	1179	8		2711
GVVKDVFAF	1179	9		2712
HADGGKVPIK	878	10	0.0003	2713
HCPALVTY	267	8		2714
HDPSPLQR	1104	8		2715
HDPSPLQRY	1104	9		2716
HFNHSGICELH	257	11		2717
HLDMLRHLY	42	9	0 0370	2718
HLREVRAVTSA	349	11		2719
HSCVDLDDK	632	9	-0.0002	2720
HSDCLACLH	249	9		2721
HSDCLACLHF	249	10		2722
HSGICELH	260	8		2723
HSGICELHCPA	260	11		2724
HTVPWDQLF	478	9		2725
HTVPWDQLFR	478	10	0.0035	2726
HVKITDFGLA	858	10		2727
HVKITDFGLAR	858	11		2728
HVRENRGR	809	8		2729
ICELHCPA	263	8		2730
IDETEYHA	872	8		2731
IDSECRPR	961	8		2732
IDSECRPRF	961	9		2733
IDSECRPRFR	961	10		2734
IDTNRSRA	184	8		2735
IDTNRSRACH	184	10		2736
IDVYMIMVK	949	9		2737
IFHKNNQLA	172	9		2738
ILDEAYVMA	767	9		2739
ILIKRRQQK	673	9	0.3800	2740
ILIKRRQQKIR	673	11		2741
ILKETELR	714	8		2742

TableXVI
HER2/NEU A03 Motif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*0301	SEQ ID NO.
ILKETELRK	714	9	0.0190	2743
ILKETELRKVK	714	11		2744
ILKGGVLIQR	148	10	0.0400	2745
ILLVVVLGVVF	661	11		2746
ILRRRFTH	894	8		2747
ILWKDIFH	167	8		2748
ILWKDIFHK	167	9	0.2800	2749
ISWLGLRSLR	450	10	0.0410	2750
ITDFGLAR	861	8		2751
ITGYLYISA	406	9		2752
IVRGTQLF	101	8		2753
KANKEILDEA	762	10		2754
KANKEILDEAY	762	11		2755
KCSKPCAR	333	8		2756
KCSKPCARVCY	333	11		2757
KCWMIDSECR	957	10		2758
KDIFHKNNQLA	170	11		2759
KDPPFCVA	591	8		2760
KDPPFCVAR	591	9		2761
KDVFAFGGA	1182	9		2762
KFPDEEGA	615	8		2763
KGCPAEQR	640	8		2764
KGCPAEQRA	640	9		2765
KGGVLIQR	150	8		2766
KGLQSLPTH	1096	9		2767
KGMSYLEDVR	831	10		2768
KGPLPTDCCH	228	10		2769
KGTPTAENPEY	1238	11		2770
KIFGSLAF	369	8		2771
KIPVAIKVLR	747	10	0.0009	2772
KIRKYTMR	681	8	0.0010	2773
KIRKYTMRR	681	9	0.7600	2774
KITDFGLA	860	8		2775
KITDFGLAR	860	9	0.1700	2776
KLRLPASPETH	32	11		2777
KSPNHVKITDF	854	11		2778
KVKVLGSGA	722	9		2779
KVKVLGSGAF	722	10		2780
KVLGSGAF	724	8		2781
KVLRENTSPK	753	10	0.3800	2782
KVLRENTSPKA	753	11		2783
KVPIKWMA	883	8		2784
LAARNVLVK	846	9	0.0580	2785
LACHQLCA	509	8		2786
LACHQLCAR	509	9	-0.0002	2787
LACHQLCARGH	509	11		2788
LACLHFNH	253	8		2789
LAFLPESF	374	8		2790
LALHHHNTH	465	9		2791
LALLPPGA	13	8		2792

Table XVI
HER2/NEU A03 Motif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*0301	SEQ ID NO.
LALLPPGAA	13	9		2793
LALTLIDTNR	179	10	-0.0002	2794
LCRWGLLLA	6	9		2795
LCYQDTILWK	161	10	0.0081	2796
LDDKGCPA	637	8		2797
LDDKGCPAEQR	637	11		2798
LDEAYVMA	768	8		2799
LDHVRENR	807	8		2800
LDHVRENRGR	807	10		2801
LDIDETEY	870	8		2802
LDIDETEYH	870	9		2803
LDIDETEYHA	870	10		2804
LDMLRHLY	43	8		2805
LFEDNYALA	107	9		2806
LFRNPHQA	485	8		2807
LFRNPHQALLH	485	11		2808
LGISWLGLR	448	9		2809
LGLEPSEEEA	1061	10		2810
LGMEHLREVR	345	10		2811
LGMEHLREVRA	345	11		2812
LGPASPLDSTF	994	11		2813
LGSGAFGTVY	726	10	0.0003	2814
LGSGAFGTVYK	726	11		2815
LGSGLALIH	461	9		2816
LGSGLALIHH	461	10		2817
LGVVFGILIK	667	10		2818
LGVVFGILIKR	667	11		2819
LIAHNQVR	85	8		2820
LIDTNRSR	183	8		2821
LIDTNRSRA	183	9		2822
LIDTNRSRACH	183	11		2823
LIHHNTHLCF	467	10		2824
LIKRRQQK	674	8		2825
LIKRRQQKIR	674	10	0.0002	2826
LIKRRQQKIRK	674	11		2827
LIQRNPQLCY	154	10	0 0012	2828
LLALLPPGA	12	9		2829
LLALLPPGAA	12	10		2830
LLDHVRENR	806	9	0.0370	2831
LLDHVRENRGR	806	11		2832
LLDIDETEY	869	9	0.0003	2833
LLDIDETEYH	869	10		2834
LLDIDETEYHA	869	11		2835
LLLALLPPGA	11	10		2836
LLLALLPPGAA	11	11		2837
LLNWCMQIA	822	9		2838
LLNWCMQIAK	822	10	0.1400	2839
LLVVVLGVVF	662	10		2840
LMPYGCLLDH	800	10		2841
LMTFGAKPY	915	9	0.0002	2842

Table XVI

HER2/NEU A03 Motif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*0301	SEQ ID NO.
LSPGKNGVVK	1173	10	-0 0002	2843
LSVFQNLQVIR	422	11		2844
LSYMPIWK	608	8		2845
LSYMPIWKF	608	9		2846
LTCSPQPEY	1131	9	0.0001	2847
LTLIDTNR	181	8		2848
LTLIDTNRSR	181	10	0.0002	2849
LTLIDTNRSRA	181	11		2850
LTPQGGAA	1197	8		2851
LTPSGAMPNQA	700	11		2852
LTRTVCAGGCA	215	11		2853
LTYLPTNA	62	8		2854
LVEPLTPSGA	696	10		2855
LVIIRDLAA	841	8		2856
LVIIRDLAAR	841	9	0.0040	2857
LVKSPNHVK	852	9	0 4800	2858
LVPQQGFF	1024	8		2859
LVSEFSRMA	972	9		2860
LVSEFSRMAR	972	10	0.0072	2861
LVTQLMPY	796	8		2862
LVTYNTDTF	271	9		2863
LVVVLGVVF	663	9		2864
MAGVGSPY	774	8		2865
MAGVGSPYVSR	774	11		2866
MALESILR	889	8		2867
MALESILRR	889	9	0.0034	2868
MALESILRRR	889	10	0.0011	2869
MALESILRRRF	889	11		2870
MARDPQRF	979	8		2871
MGDLVDAEEY	1014	10	0.0002	2872
MIDSECRPR	960	9	0 0017	2873
MIDSECRPRF	960	10		2874
MIDSECRPRFR	960	11		2875
MSYLEDVR	833	8		2876
MSYLEDVRLVH	833	11		2877
MTFGAKPY	916	8		2878
NARHCLPCH	556	9		2879
NGSVTCFGPEA	571	11		2880
NGVVKDVF	1178	8		2881
NGVVKDVFA	1178	9		2882
NGVVKDVFAF	1178	10		2883
NIQEFAGCK	360	9	0.0002	2884
NIQEFAGCKK	360	10	0.0003	2885
NLELTYLPTNA	59	11		2886
NLQVIRGR	427	8		2887
NLQVIRGRILH	427	11		2888
NTHLCFVH	471	8		2889
NTSPKANK	758	8		2890
NTTPVTGA	125	8		2891
NVKIPVAIK	745	9	0.0058	2892

Table XVI
HER2/NEU A03 Motif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*0301	SEQ ID NO.
NVLVKSPNH	850	9		2893
NVLVKSPNHVK	850	11		2894
PAARPAGA	1158	8		2895
PAFDNLYY	1215	8		2896
PAFSPAFDNLY	1211	11		2897
PAGATLER	1162	8		2898
PAGATLERPK	1162	10	-0 0002	2899
PALVTYNTDTF	269	11		2900
PAPGAGGMVH	1035	10		2901
PAPGAGGMVHH	1035	11		2902
PAREIPDLLEK	927	11		2903
PASPLDSTF	996	9		2904
PASPLDSTFY	996	10	0.0003	2905
PASPLDSTFYR	996	11		2906
PCPINCTH	625	8		2907
PCSPMCKGSR	194	10		2908
PDGENVKIPVA	741	11		2909
PDLLEKGER	932	9		2910
PDLSYMPIWK	606	10		2911
PDLSYMPIWKF	606	11		2912
PDSLPDLSVF	416	10		2913
PDVRPQPPSPR	1143	11		2914
PGAGGMVH	1037	8		2915
PGAGGMVHH	1037	9		2916
PGAGGMVHHR	1037	10		2917
PGAGGMVHHRH	1037	11		2918
PGGLRELQLR	134	10		2919
PGKNGVVK	1175	8		2920
PGKNGVVKDVF	1175	11		2921
PICTIDVY	945	8		2922
PIWKFPDEEGA	612	11		2923
PLAPSEGA	1074	8		2924
PLDSTFYR	999	8		2925
PLHNQEVTA	316	9		2926
PLNNTTPVTGA	122	11		2927
PLPAARPA	1156	8		2928
PLPAARPAGA	1156	10		2929
PLPSETDGY	1119	9	0.0002	2930
PLPSETDGYVA	1119	11		2931
PLPTDCCH	230	8		2932
PLQPEQLQVF	391	10		2933
PLQRLRIVR	95	9	0.0002	2934
PLTCSPQPEY	1130	10	0.0002	2935
PLTSIISA	650	8		2936
PSEEEAPR	1065	8		2937
PSEGAGSDVF	1077	10		2938
PSETDGYVA	1121	9		2939
PSGAMPNQA	702	9		2940
PSGVKPDLSY	601	10	0.0003	2941
PSPREGPLPA	1150	10		2942

Table XVI
HER2/NEU A03 Motif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*0301	SEQ ID NO.
PSPREGPLPAA	1150	11		2943
PSTFKGTPTA	1234	10		2944
PTAENPEY	1241	8		2945
PTDCCHEQCA	232	10		2946
PTDCCHEQCAA	232	11		2947
PTHDPSPLQR	1102	10	0.0003	2948
PTHDPSPLQRY	1102	11		2949
PTNASLSF	66	8		2950
PTQCVNCSQF	525	10		2951
PVAIKVLR	749	8		2952
PVTGASPGGLR	128	11		2953
QALLHTANR	491	9	0.0046	2954
QAQMRILK	709	8		2955
QCAAGCTGPK	239	10		2956
QCAAGCTGPKH	239	11		2957
QCVACAHY	583	8		2958
QCVACAHYK	583	9		2959
QCVNCSQF	527	8		2960
QCVNCSQFLR	527	10		2961
QDIQEVQGY	75	9		2962
QDLLNWCMQIA	820	11		2963
QDPPERGA	1225	8		2964
QDTILWKDIF	164	10		2965
QDTILWKDIFH	164	11		2966
QGFFCPDPA	1028	9		2967
QGGAAPQPH	1200	9		2968
QGLGISWLGLR	446	11		2969
QGLPREYVNA	548	10		2970
QGLPREYVNAR	548	11		2971
QGNLELTY	57	8		2972
QGYVLIAH	81	8		2973
QIAKGMSY	828	8		2974
QLALTLIDTNR	178	11		2975
QLCYQDTILWK	160	11		2976
QLFEDNYA	106	8		2977
QLFEDNYALA	106	10		2978
QLFRNPHQA	484	9		2979
QLMPYGCLLDH	799	11		2980
QLRSLTEILK	141	10	0.2000	2981
QLVTQLMPY	795	9	0.0110	2982
QMRILKETELR	711	11		2983
QSLTRTVCA	213	9		2984
QVCTGTDMK	24	9	0.0007	2985
QVCTGTDMKLR	24	11		2986
QVIRGRILH	429	9		2987
QVPLQRLR	93	8		2988
QVPLQRLRIVR	93	11		2989
QVRQVPLQR	90	9	0.0029	2990
QVRQVPLQRLR	90	11		2991
QVVQGNLELTY	54	11		2992

Table XVI
HER2/NEU A03 Motif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*0301	SEQ ID NO.
RACHPCSPMCK	190	11		2993
RASPLTSHSA	647	11		2994
RAVTSANIQEF	354	11		2995
RCEKCSKPCA	330	10		2996
RCEKCSKPCAR	330	11		2997
RDLAARNVLVK	844	11		2998
RFRELVSEF	968	9		2999
RFRELVSEFSR	968	11		3000
RFTHQSDVWSY	898	11		3001
RGAPPSTF	1230	8		3002
RGAPPSTFK	1230	9		3003
RGQECVEECR	536	10		3004
RGRILHNGA	432	9		3005
RGRILHNGAY	432	10		3006
RGTQLFEDNY	103	10	0.0003	3007
RGTQLFEDNYA	103	11		3008
RILHNGAY	434	8		3009
RILKETELR	713	9	0.0007	3010
RILKETELRK	713	10	0.0570	3011
RIVRGTQLF	100	9		3012
RLLDIDETEY	868	10	0.0017	3013
RLLDIDETEYH	868	11		3014
RLPASPETH	34	9		3015
RLRIVRGTQLF	98	11		3016
RLVHRDLA	840	8		3017
RLVHRDLAA	840	9		3018
RLVHRDLAAR	840	10	0.1800	3019
RMARDPQR	978	8		3020
RMARDPQRF	978	9	0.0001	3021
RSLRELGSGLA	456	11		3022
RSLTEILK	143	8		3023
RSPLAPSEGA	1072	10		3024
RTVCAGGCA	217	9		3025
RTVCAGGCAR	217	10	0.0068	3026
RVCYGLGMEH	340	10		3027
RVLQGLPR	545	8		3028
RVLQGLPREY	545	10	0.0350	3029
SANIQEFA	358	8		3030
SANIQEFAGCK	358	11		3031
SCTLVCPLH	310	9		3032
SCVDLDDK	633	8		3033
SCVTACPY	294	8		3034
SCVTACPYNY	294	10		3035
SDCLACLH	250	8		3036
SDCLACLHF	250	9		3037
SDCLACLHFNH	250	11		3038
SFDGDPASNTA	380	11		3039
SGAFGTVY	728	8		3040
SGAFGTVYK	728	9		3041
SGAMPNQA	703	8		3042

Table XVI
HER2/NEU A03 Motif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*0301	SEQ ID NO.
SGAMPNQAQMR	703	11		3043
SGICELHCPA	261	10		3044
SGLALIHH	463	8		3045
SGLALIHHINTH	463	11		3046
SGVKPDLSY	602	9		3047
SILRRRFTH	893	9		3048
SLAFLPESF	373	9		3049
SLPDLSVF	418	8		3050
SLRELGSGLA	457	10		3051
SLTRTVCA	214	8		3052
SMPNPEGR	281	8		3053
SMPNPEGRY	281	9	0.0002	3054
SMPNPEGRYTF	281	11		3055
SSEDCQSLTR	208	10	-0.0002	3056
STFKGTPTA	1235	9		3057
STQVCTGTDMK	22	11		3058
SVFQNLQVIR	423	10	0.0170	3059
SVTCFGPEA	573	9		3060
TAEDGTQR	323	8		3061
TAEDGTQRCEK	323	11		3062
TCSPQPEY	1132	8		3063
TDCCHEQCA	233	9		3064
TDCCHEQCAA	233	10		3065
TDMKLRLPA	29	9		3066
TFESMPNPEGR	278	11		3067
TFGASCVTA	290	9		3068
TFKGTPTA	1236	8		3069
TGASPGGLR	130	9		3070
TGPKHSDCLA	245	10		3071
TGTDMKLR	27	8		3072
TGTDMKLRLPA	27	11		3073
TGYLYISA	407	8		3074
TIDVYMIMVK	948	10	0.0130	3075
TILWKDIF	166	8		3076
TILWKDIFH	166	9		3077
TILWKDIFHK	166	10	0.0430	3078
TLEEITGY	402	8		3079
TLEEITGYLY	402	10	0.0001	3080
TLGLEPSEEEA	1060	11		3081
TLIDTNRSR	182	9	0.0004	3082
TLIDTNRSRA	182	10		3083
TLSPGKNGVVK	1172	11		3084
TSANIQEF	357	8		3085
TSANIQEFA	357	9		3086
TVCAGGCA	218	8		3087
TVCAGGCAR	218	9	0.0004	3088
TVCAGGCARCK	218	11		3089
TVPLPSETDGY	1117	11		3090
TVPWDQLF	479	8		3091
TVPWDQLFR	479	9	0.0006	3092

Table XVI
HER2/NEU A03 Motif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*0301	SEQ ID NO.
TVQLVTQLMPY	793	11		3093
TVWELMTF	911	8		3094
TVWELMTFGA	911	10		3095
TVWELMTFGAK	911	11		3096
VACAHYKDPPF	585	11		3097
VARCPSGVK	·597	9	0.0100	3098
VCAGGCAR	219	8		3099
VCAGGCARCK	219	10		3100
VCPLHNQEVTA	314	11		3101
VCTGTDMK	25	8		3102
VCTGTDMKLR	25	10		3103
VCYGLGMEH	341	9		3104
VCYGLGMEHLR	341	11		3105
VDLDDKGCPA	635	10		3106
VFDGDLGMGA	1085	10		3107
VFDGDLGMGAA	1085	11		3108
VFETLEEITGY	399	11		3109
VFGILKR	670	8		3110
VFGILKRR	670	9		3111
VFQNLQVIR	424	9		3112
VFQNLQVIRGR	424	11		3113
VGEGLACH	505	8		3114
VGSCTLVCPLH	308	11		3115
VGSPYVSR	777	8		3116
VIQNEDLGPA	988	10		3117
VIRGRILH	430	8		3118
VIRGRILHNGA	430	11		3119
VLGSGAFGTVY	725	11		3120
VLGVVFGILIK	666	11		3121
VLIAHNQVR	84	9	0.0033	3122
VLIQRNPQLCY	153	11		3123
VLQGLPREY	546	9	0.0012	3124
VLRENTSPK	754	9	0 4000	3125
VLRENTSPKA	754	10		3126
VLVKSPNH	851	8		3127
VLVKSPNHVK	851	10	0.0820	3128
VMAGVGSPY	773	9	0.0580	3129
VSEFSRMA	973	8		3130
VSEFSRMAR	973	9	-0.0002	3131
VTACPYNY	296	8		3132
VTAEDGTQR	322	9	0.0002	3133
VTCFGPEA	574	8		3134
VTGASPGGLR	129	10	0.0002	3135
VTSANIQEF	356	9		3136
VTSANIQEFA	356	10		3137
VTVWELMTF	910	9		3138
VTVWELMTFGA	910	11		3139
VTYNTDTF	272	8		3140
VVFGILIK	669	8		3141
VVFGILIKR	669	9	0.1100	3142

Table XVI
HER2/NEU A03 Motif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*0301	SEQ ID NO.
VVFGILIKRR	669	10	0.0030	3143
VVIQNEDLGPA	987	11		3144
VVKDVFAF	1180	8		3145
VVKDVFAFGGA	1180	11		3146
VVQGNLELTY	55	10	0.0024	3147
VVVLGVVF	664	8		3148
WCMQIAKGMSY	825	11		3149
WDQDPPER	1223	8		3150
WDQDPPERGA	1223	10		3151
WDQLFRNPH	482	9		3152
WDQLFRNPHQA	482	11		3153
WIPDGENVK	739	9	0 0002	3154
WLGLRSLR	452	8		3155
WMALESILR	888	9	-0.0002	3156
WMALESILRR	888	10	0.0085	3157
WMALESILRRR	888	11		3158
WMIDSECR	959	8		3159
WMIDSECRPR	959	10	-0.0002	3160
WMIDSECRPRF	959	11		3161
YGCLLDHVR	803	9		3162
YGLGMEHLR	343	9		3163
YGVTVWELMTF	908	11		3164
YLEDVRLVH	835	9		3165
YLEDVRLVHR	835	10	0 0003	3166
YLPTNASLSF	64	10		3167
YLTPQGGA	1196	8		3168
YLTPQGGAA	1196	9		3169
YLVPQQGF	1023	8		3170
YLVPQQGFF	1023	9		3171
YTFGASCVTA	289	10		3172
YVLIAHNQVR	83	10	0.0043	3173
YVMAGVGSPY	772	10	0 0100	3174
YVNARHCLPCH	554	11		3175
YVNQPDVR	1139	8		3176

TableXVII
HER2/NEU A11 Motif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*1101	SEQ ID NO.
AAGCTGPK	241	8		3177
AAGCTGPKH	241	9		3178
AAKGLQSLPTH	1094	11		3179
AARNVLVK	847	8		3180
AARPAGATLER	1159	11		3181
ACHPCSPMCK	191	10		3182
ACHQLCAR	510	8		3183
ACHQLCARGH	510	10		3184
ACQPCPINCTH	622	11		3185
ADGGKVPIK	879	9		3186
ADQCVACAH	581	9		3187
ADQCVACAHY	581	10		3188
ADQCVACAHYK	581	11		3189
AFGGAVENPEY	1186	11		3190
AFSPAFDNLY	1212	10	0.0003	3191
AFSPAFDNLYY	1212	11		3192
AGATLERPK	1163	9		3193
AGCTGPKH	242	8		3194
AGGCARCK	221	8		3195
AGGMVHHR	1039	8		3196
AGGMVHHRH	1039	9		3197
AGGMVHHRHR	1039	10		3198
AGVGSPYVSR	775	10		3199
ALESILRR	890	8		3200
ALESILRRR	890	9	0.0006	3201
ALHHHNTH	466	8		3202
ALLHTANR	492	8		3203
ALTLIDTNR	180	9	0.0005	3204
ALTLIDTNRSR	180	11		3205
AMPNQAQMR	705	9	0.0006	3206
ANIQEFAGCK	359	10		3207
ANIQEFAGCKK	359	11		3208
ANKEILDEAY	763	10		3209
ASCVTACPY	293	9	0.0074	3210
ASCVTACPYNY	293	11		3211
ASPETHLDMLR	37	11		3212
ASPLDSTFY	997	9	0.0004	3213
ASPLDSTFYR	997	10	0.0670	3214
CAAGCTGPK	240	9	0.0021	3215
CAAGCTGPKH	240	10		3216
CAGGCARCK	220	9	-0.0002	3217
CLACLHFNH	252	9		3218
CLLDHVRENR	805	10	0.0001	3219
CMQIAKGMSY	826	10	0.0001	3220
CSKPCARVCY	334	10	0.0002	3221
CSPMCKGSR	195	9	-0.0001	3222
CTGTDMKLR	26	9	0.0005	3223
CTHSCVDLDDK	630	11		3224
CTIDVYMIMVK	947	11		3225
CTLVCPLH	311	8		3226

TableXVII
HER2/NEU A11 Motif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*1101	SEQ ID NO.
CVACAHYK	584	8		3227
CVARCPSGVK	596	10	0.0042	3228
CVGEGLACH	504	9		3229
CVNCSQFLR	528	9	0.0310	3230
CVTACPYNY	295	9	0 0004	3231
DCLACLHFNH	251	10		3232
DDKGCPAEQR	638	10		3233
DGDLGMGAAK	1087	10		3234
DGGKVPIK	880	8		3235
DGTQRCEK	326	8		3236
DGTQRCEKCSK	326	11		3237
DIDETEYH	871	8		3238
DIQEVQGY	76	8		3239
DLAARNVLVK	845	10	0.0007	3240
DLGMGAAK	1089	8		3241
DLLEKGER	933	8		3242
DLLNWCMQIAK	821	11		3243
DLSYMPIWK	607	9	0.0100	3244
DLVDAEEY	1016	8		3245
DMGDLVDAEEY	1013	11		3246
DSECRPRFR	962	9	-0.0002	3247
DTILWKDIFH	165	10		3248
DTILWKDIFHK	165	11		3249
DTNRSRACH	185	9		3250
DVRPQPPSPR	1144	10	0.0001	3251
DVYMIMVK	950	8		3252
EADQCVACAH	580	10		3253
EADQCVACAHY	580	11		3254
ECRVLQGLPR	543	10		3255
ECVGEGLACH	503	10		3256
EDCQSLTR	210	8		3257
EDGTQRCEK	325	9		3258
EDVRLVHR	837	8		3259
EFSRMARDPQR	975	11		3260
EGLACHQLCAR	507	11		3261
EGPLPAAR	1154	8		3262
EILKGGVLIQR	147	11		3263
EIPDLLEK	930	8		3264
EIPDLLEKGER	930	11		3265
ELGSGLALIH	460	10		3266
ELGSGLALIHH	460	11		3267
ELHCPALVTY	265	10	0.0002	3268
ELMTFGAK	914	8		3269
ELMTFGAKPY	914	10	0.0002	3270
ELVSEFSR	971	8		3271
ELVSEFSRMAR	971	11		3272
ENTSPKANK	757	9		3273
ENVKIPVAIK	744	10		3274
ESILRRRFTH	892	10		3275
ESMPNPEGR	280	9	-0.0002	3276

TableXVII
HER2/NEU A11 Motif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*1101	SEQ ID NO.
ESMPNPEGRY	280	10	0.0003	3277
ESSEDCQSLTR	207	11		3278
ETELRKVK	717	8		3279
ETEYHADGGK	874	10	0.0001	3280
ETHLDMLR	40	8		3281
ETHLDMLRH	40	9		3282
ETHLDMLRHLY	40	11		3283
ETLEEITGY	401	9	0.0002	3284
ETLEEITGYLY	401	11		3285
EVQGYVLIAH	79	10		3286
EVTAEDGTQR	321	10	0.0001	3287
FCVARCPSGVK	595	11		3288
FDGDLGMGAAK	1086	11		3289
FGASCVTACPY	291	11		3290
FGGAVENPEY	1187	10		3291
FGILIKRR	671	8		3292
FGILIKRRQQK	671	11		3293
FLQDIQEVQGY	73	11		3294
FNHSGICELH	258	10		3295
FSPAFDNLY	1213	9	0.0002	3296
FSPAFDNLYY	1213	10	0.0010	3297
FSRMARDPQR	976	10	0.0010	3298
FTHQSDVWSY	899	10	0.0005	3299
GAFGTVYK	729	8		3300
GAGGMVHH	1038	8		3301
GAGGMVHHR	1038	9	0.0043	3302
GAGGMVHHRH	1038	10		3303
GAGGMVHHRHR	1038	11		3304
GAKPYDGIPAR	919	11		3305
GAMPNQAQMR	704	10	0.0041	3306
GAPPSTFK	1231	8		3307
GASCVTACPY	292	10	0.0001	3308
GASPGGLR	131	8		3309
GATLERPK	1164	8		3310
GAVENPEY	1189	8		3311
GCLLDHVR	804	8		3312
GCLLDHVRENR	804	11		3313
GDLGMGAAK	1088	9		3314
GDLVDAEEY	1015	9		3315
GGAAPQPH	1201	8		3316
GGAVENPEY	1188	9	0.0001	3317
GGLRELQLR	135	9		3318
GGMVHHRH	1040	8		3319
GGMVHHRHR	1040	9		3320
GILIKRRQQK	672	10	0.0014	3321
GISWLGLR	449	8		3322
GISWLGLRSLR	449	11		3323
GIWIPDGENVK	737	11		3324
GLACHQLCAR	508	10	0.0001	3325
GLALHHHNTH	464	10		3326

TableXVII
HER2/NEU A11 Motif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*1101	SEQ ID NO.
GLEPSEEEAPR	1062	11		3327
GLGISWLGLR	447	10	0.0001	3328
GLGMEHLR	344	8		3329
GLGMEHLREVR	344	11		3330
GLPREYVNAR	549	10	0.0003	3331
GLPREYVNARH	549	11		3332
GLQSLPTH	1097	8		3333
GLRELQLR	136	8		3334
GMEHLREVR	346	9	-0.0002	3335
GMSYLEDVR	832	9	0.0002	3336
GMVHHRHR	1041	8		3337
GSCTLVCPLH	309	10		3338
GSGAFGTVY	727	9	0.0001	3339
GSGAFGTVYK	727	10	0.1300	3340
GSGLALIH	462	8		3341
GSGLALIHH	462	9		3342
GTPTAENPEY	1239	10	0.0022	3343
GTQLFEDNY	104	9	0.0280	3344
GTQRCEKCSK	327	10	0.6100	3345
GVGSPYVSR	776	9	0.0066	3346
GVKPDLSY	603	8		3347
GVVFGILIK	668	9	0.0890	3348
GVVFGILIKR	668	10	0.0330	3349
GVVFGILIKRR	668	11		3350
HADGGKVPIK	878	10	0.0008	3351
HCPALVTY	267	8		3352
HDPSPLQR	1104	8		3353
HDPSPLQRY	1104	9		3354
HFNHSGICELH	257	11		3355
HLDMLRHLY	42	9	0 0002	3356
HNQVRQVPLQR	88	11		3357
HNTHLCFVH	470	9		3358
HSCVDLDDK	632	9	0 0007	3359
HSDCLACLH	249	9		3360
HSGICELH	260	8		3361
HTVPWDQLFR	478	10	0.0720	3362
HVKITDFGLAR	858	11		3363
HVRENRGR	809	8		3364
IDSECRPR	961	8		3365
IDSECRPRFR	961	10		3366
IDTNRSRACH	184	10		3367
IDVYMIMVK	949	9		3368
ILIKRRQQK	673	9	0.0097	3369
ILIKRRQQKIR	673	11		3370
ILKETELR	714	8		3371
ILKETELRK	714	9	0.0023	3372
ILKETELRKVK	714	11		3373
ILKGGVLIQR	148	10	0.0005	3374
ILRRRFTH	894	8		3375
ILWKDIFH	167	8		3376

TableXVII
HER2/NEU A11 Motif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*1101	SEQ ID NO.
ILWKDIFHK	167	9	0.3100	3377
ISWLGLRSLR	450	10	0.0027	3378
ITDFGLAR	861	8		3379
KANKEILDEAY	762	11		3380
KCSKPCAR	333	8		3381
KCSKPCARVCY	333	11		3382
KCWMIDSECR	957	10		3383
KDPPFCVAR	591	9		3384
KGCPAEQR	640	8		3385
KGGVLIQR	150	8		3386
KGLQSLPTH	1096	9		3387
KGMSYLEDVR	831	10		3388
KGPLPTDCCH	228	10		3389
KGTPTAENPEY	1238	11		3390
KIPVAIKVLR	747	10	0.0099	3391
KIRKYTMR	681	8	0.0004	3392
KIRKYTMRR	681	9	0.0018	3393
KITDFGLAR	860	9	0.2400	3394
KLRLPASPETH	32	11		3395
KVLRENTSPK	753	10	0.2200	3396
LAARNVLVK	846	9	0.0285	3397
LACHQLCAR	509	9	0.0003	3398
LACHQLCARGH	509	11		3399
LACLHFNH	253	8		3400
LALIHHNTH	465	9		3401
LALTLIDTNR	179	10	0.0003	3402
LCYQDTILWK	161	10	0.0063	3403
LDDKGCPAEQR	637	11		3404
LDHVRENR	807	8		3405
LDHVRENRGR	807	10		3406
LDIDETEY	870	8		3407
LDIDETEYH	870	9		3408
LDMLRHLY	43	8		3409
LFRNPHQALLH	485	11		3410
LGISWLGLR	448	9		3411
LGMEHLREVR	345	10		3412
LGSGAFGTVY	726	10	0.0003	3413
LGSGAFGTVYK	726	11		3414
LGSGLALIH	461	9		3415
LGSGLALIHH	461	10		3416
LGVVFGILIK	667	10		3417
LGVVFGILIKR	667	11		3418
LIAHNQVR	85	8		3419
LIDTNRSR	183	8		3420
LIDTNRSRACH	183	11		3421
LIKRRQQK	674	8		3422
LIKRRQQKIR	674	10	0.0001	3423
LIKRRQQKIRK	674	11		3424
LIQRNPQLCY	154	10	0.0002	3425
LLDHVRENR	806	9	0.0006	3426

TableXVII
HER2/NEU A11 Motif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*1101	SEQ ID NO.
LLDHVRENRGR	806	11		3427
LLDIDETEY	869	9	0.0001	3428
LLDIDETEYH	869	10		3429
LLNWCMQIAK	822	10	0.1400	3430
LMPYGCLLDH	800	10		3431
LMTFGAKPY	915	9	0.0003	3432
LNWCMQIAK	823	9		3433
LSPGKNGVVK	1173	10	0.0003	3434
LSVFQNLQVIR	422	11		3435
LSYMPIWK	608	8		3436
LTCSPQPEY	1131	9	0.0061	3437
LTLIDTNR	181	8		3438
LTLIDTNRSR	181	10	0.0005	3439
LVHRDLAAR	841	9	0.0014	3440
LVKSPNHVK	852	9	0.0700	3441
LVSEFSRMAR	972	10	0.0330	3442
LVTQLMPY	796	8		3443
MAGVGSPY	774	8		3444
MAGVGSPYVSR	774	11		3445
MALESILR	889	8		3446
MALESILRR	889	9	0.0237	3447
MALESILRRR	889	10	0.0003	3448
MGDLVDAEEY	1014	10	0.0002	3449
MIDSECRPR	960	9	0.0006	3450
MIDSECRPRFR	960	11		3451
MSYLEDVR	833	8		3452
MSYLEDVRLVH	833	11		3453
MTFGAKPY	916	8		3454
NARHCLPCH	556	9		3455
NIQEFAGCK	360	9	0.0036	3456
NIQEFAGCKK	360	10	0.0056	3457
NLQVIRGR	427	8		3458
NLQVIRGRILH	427	11		3459
NTHLCFVH	471	8		3460
NTSPKANK	758	8		3461
NVKIPVAIK	745	9	0.0007	3462
NVLVKSPNH	850	9		3463
NVLVKSPNHVK	850	11		3464
PAFDNLYY	1215	8		3465
PAFSPAFDNLY	1211	11		3466
PAGATLER	1162	8		3467
PAGATLERPK	1162	10	-0.0002	3468
PAPGAGGMVH	1035	10		3469
PAPGAGGMVHH	1035	11		3470
PAREIPDLLEK	927	11		3471
PASPLDSTFY	996	10	0.0001	3472
PASPLDSTFYR	996	11		3473
PCPINCTH	625	8		3474
PCSPMCKGSR	194	10		3475
PDLLEKGER	932	9		3476

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HER2/NEU A11 Motif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*1101	SEQ ID NO.
PDLSYMPIWK	606	10		3477
PDVRPQPPSPR	1143	11		3478
PGAGGMVH	1037	8		3479
PGAGGMVHH	1037	9		3480
PGAGGMVHHR	1037	10		3481
PGAGGMVHHRH	1037	11		3482
PGGLRELQLR	134	10		3483
PGKNGVVK	1175	8		3484
PICTIDVY	945	8		3485
PLDSTFYR	999	8		3486
PLPSETDGY	1119	9	0.0002	3487
PLPTDCCH	230	8		3488
PLQRLRIVR	95	9	0.0001	3489
PLTCSPQPEY	1130	10	0.0002	3490
PNQAQMRILK	707	10		3491
PSEEEAPR	1065	8		3492
PSGVKPDLSY	601	10	0.0003	3493
PTAENPEY	1241	8		3494
PTHDPSPLQR	1102	10	0.0001	3495
PTHDPSPLQRY	1102	11		3496
PVAIKVLR	749	8		3497
PVTGASPGGLR	128	11		3498
QALLHTANR	491	9	0.0010	3499
QAQMRILK	709	8		3500
QCAAGCTGPK	239	10		3501
QCAAGCTGPKH	239	11		3502
QCVACAHY	583	8		3503
QCVACAHYK	583	9		3504
QCVNCSQFLR	527	10		3505
QDIQEVQGY	75	9		3506
QDTILWKDIFH	164	11		3507
QGGAAPQPH	1200	9		3508
QGLGISWLGLR	446	11		3509
QGLPREYVNAR	548	11		3510
QGNLELTY	57	8		3511
QGYVLIAH	81	8		3512
QIAKGMSY	828	8		3513
QLALTLIDTNR	178	11		3514
QLCYQDTILWK	160	11		3515
QLMPYGCLLDH	799	11		3516
QLRSLTEILK	141	10	0.0130	3517
QLVTQLMPY	795	9	0.0039	3518
QMRILKETELR	711	11		3519
QNLQVIRGR	426	9		3520
QVCTGTDMK	24	9	0.0520	3521
QVCTGTDMKLR	24	11		3522
QVIRGRILH	429	9		3523
QVPLQRLR	93	8		3524
QVPLQRLRIVR	93	11		3525
QVRQVPLQR	90	9	0.0005	3526

TableXVII

HER2/NEU A11 Motif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*1101	SEQ ID NO.
QVRQVPLQRLR	90	11		3527
QVVQGNLELTY	54	11		3528
RACHPCSPMCK	190	11		3529
RCEKCSKPCAR	330	11		3530
RDLAARNVLVK	844	11		3531
RFRELVSEFSR	968	11		3532
RFTHQSDVWSY	898	11		3533
RGAPPSTFK	1230	9		3534
RGQECVEECR	536	10		3535
RGRILHNGAY	432	10		3536
RGTQLFEDNY	103	10	0.0015	3537
RILHNGAY	434	8		3538
RILKETELR	713	9	0.0038	3539
RILKETELRK	713	10	0.1100	3540
RLLDIDETEY	868	10	0.0001	3541
RLLDIDETEYH	868	11		3542
RLPASPETH	34	9		3543
RLVHRDLAAR	840	10	0.0001	3544
RMARDPQR	978	8		3545
RNPHQALLH	487	9		3546
RNVLVKSPNH	849	10		3547
RSLTEILK	143	8		3548
RTVCAGGCAR	217	10	0.0130	3549
RVCYGLGMEH	340	10		3550
RVLQGLPR	545	8		3551
RVLQGLPREY	545	10	0.0050	3552
SANIQEFAGCK	358	11		3553
SCTLVCPLH	310	9		3554
SCVDLDDK	633	8		3555
SCVTACPY	294	8		3556
SCVTACPYNY	294	10		3557
SDCLACLH	250	8		3558
SDCLACLHFNH	250	11		3559
SGAFGTVY	728	8		3560
SGAFGTVYK	728	9		3561
SGAMPNQAQMR	703	11		3562
SGLALIHH	463	8		3563
SGLALIHHNTH	463	11		3564
SGVKPDLSY	602	9		3565
SILRRRFTH	893	9		3566
SMPNPEGR	281	8		3567
SMPNPEGRY	281	9	0.0003	3568
SSEDCQSLTR	208	10	0.0020	3569
STQVCTGTDMK	22	11		3570
SVFQNLQVIR	423	10	0.0750	3571
TAEDGTQR	323	8		3572
TAEDGTQRCEK	323	11		3573
TCSPQPEY	1132	8		3574
TFESMPNPEGR	278	11		3575
TGASPGGLR	130	9		3576

TableXVII
HER2/NEU A11 Motif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*1101	SEQ ID NO.
TGTDMKLR	27	8		3577
TIDVYMIMVK	948	10	0.1200	3578
TII WKDIFH	166	9		3579
TILWKDIFHK	166	10	3.6000	3580
TLEEITGY	402	8		3581
TLEEITGYLY	402	10	0.0001	3582
TLIDTNRSR	182	9	0.0005	3583
TLSPGKNGVVK	1172	11		3584
TNRSRACH	186	8		3585
TVCAGGCAR	218	9	0.0230	3586
TVCAGGCARCK	218	11		3587
TVPLPSETDGY	1117	11		3588
TVPWDQLFR	479	9	0.0072	3589
TVQLVTQLMPY	793	11		3590
TVWELMTFGAK	911	11		3591
VARCPSGVK	597	9	-0.0002	3592
VCAGGCAR	219	8		3593
VCAGGCARCK	219	10		3594
VCTGTDMK	25	8		3595
VCTGTDMKLR	25	10		3596
VCYGLGMEH	341	9		3597
VCYGLGMEHLR	341	11		3598
VFETLEEITGY	399	11		3599
VFGILIKR	670	8		3600
VFGILIKRR	670	9		3601
VFQNLQVIR	424	9		3602
VFQNLQVIRGR	424	11		3603
VGEGLACH	505	8		3604
VGSCTLVCPLH	308	11		3605
VGSPYVSR	777	8		3606
VIRGRILH	430	8		3607
VLGSGAFGTVY	725	11		3608
VLGVVFGILIK	666	11		3609
VLIAHNQVR	84	9	0.0007	3610
VLIQRNPQLCY	153	11		3611
VLQGLPREY	546	9	0.0002	3612
VLRENTSPK	754	9	0.0130	3613
VLVKSPNH	851	8		3614
VLVKSPNHVK	851	10	0.0072	3615
VMAGVGSPY	773	9	0.0079	3616
VNARHCLPCH	555	10		3617
VNCSQFLR	529	8		3618
VSEFSRMAR	973	9	0.0021	3619
VTACPYNY	296	8		3620
VTAEDGTQR	322	9	0.0140	3621
VTGASPGGLR	129	10	0.0005	3622
VVFGILIK	669	8		3623
VVFGILIKR	669	9	0.7200	3624
VVFGILIKRR	669	10	0.0160	3625
VVQGNLELTY	55	10	0 0110	3626

TableXVII
HER2/NEU A11 Motif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*1101	SEQ ID NO.
WCMQIAKGMSY	825	11		3627
WDQDPPER	1223	8		3628
WDQLFRNPH	482	9		3629
WIPDGENVK	739	9	0.0001	3630
WLGLRSLR	452	8		3631
WMALESILR	888	9	-0.0002	3632
WMALESILRR	888	10	0.0016	3633
WMALESILRRR	888	11		3634
WMIDSECR	959	8		3635
WMIDSECRPR	959	10	0.0002	3636
YGCLLDHVR	803	9		3637
YGLGMEHLR	343	9		3638
YLEDVRLVH	835	9		3639
YLEDVRLVHR	835	10	0 0001	3640
YVLIAHNQVR	83	10	0.0013	3641
YVMAGVGSPY	772	10	0.0120	3642
YVNARHCLPCH	554	11		3643
YVNQPDVR	1139	8		3644

TableXVIII
HER2/NEU A24 Motif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*2401	SEQ ID NO.
AFDNLYYW	1216	8	0.0039	3645
AFGTVYKGI	730	9	0.0002	3646
AFGTVYKGIW	730	10	0.0010	3647
AFGTVYKGIWI	730	11	0.0008	3648
AFSPAFDNL	1212	9	0.0011	3649
AMPNQAQMRI	705	10	0.0002	3650
AMPNQAQMRIL	705	11	-0.0003	3651
AWPDSLPDL	414	9	0.0041	3652
AYSLTLQGL	440	9	0.1300	3653
AYSLTLQGLGI	440	11	0.0230	3654
CFVHTVPW	475	8	0.0190	3655
CFVHTVPWDQL	475	11	0.0003	3656
CMQIAKGMSYL	826	11	-0.0003	3657
CYGLGMEHL	342	9	0.0180	3658
CYQDTILW	162	8	0.0120	3659
CYQDTILWKDI	162	11	0.0016	3660
DFGLARLL	863	8	0.0005	3661
DFGLARLLDI	863	10	0.0002	3662
EFAGCKKI	363	8	-0.0003	3663
EFAGCKKIF	363	9	0.0003	3664
EYHADGGKVPI	876	11	-0.0003	3665
EYLVPQQGF	1022	9	0.0014	3666
EYLVPQQGFF	1022	10	0.0120	3667
EYVNARHCL	553	9	0.0061	3668
GMGAAKGL	1091	8	-0.0003	3669
GMGAAKGLQSL	1091	11	-0.0003	3670
GMSYLEDVRL	832	10		3671
GYLYISAW	408	8	0.0044	3672
HFNHSGICEL	257	10	0.0002	3673
IFGSLAFL	370	8	0.0120	3674
IFHKNNQL	172	8	-0.0003	3675
IFHKNNQLAL	172	10	0.0022	3676
IMVKCWMI	954	8	0.0210	3677
IWIPDGENVKI	738	11	0.0027	3678
KWMALESI	887	8	0.0080	3679
KWMALESIL	887	9	0.0150	3680
KYTMRRLL	684	8	0.0024	3681
LFEDNYAL	107	8	0.0006	3682
LFEDNYALAVL	107	11	0.0006	3683
LFRNPHQAL	485	9	0.0002	3684
LFRNPHQALL	485	10	0.0014	3685
LMPYGCLL	800	8	0.0076	3686
LYISAWPDSL	410	10	0.0840	3687
PMCKGSRCW	197	9	0.0011	3688
PYDGIPAREI	922	10	0.0005	3689
PYVSRLLGI	780	9	0.1700	3690
PYVSRLLGICL	780	11	0.0320	3691
QMRILKETEL	711	10		3692
RFRELVSEF	968	9	0.0180	3693
RLTHQSDVW	898	9	0.0110	3694

TableXVIII
HER2/NEU A24 Motif Peptides with Binding Data

Sequence	Position	No. of Amino Acids	A*2401	SEQ ID NO.
RFVVIQNEDL	985	10	0.0002	3695
RMARDPQRF	978	9	0.0032	3696
RWGLLLAL	8	8	0.0250	3697
RWGLLLALL	8	9	1.3000	3698
RYSEDPTVPL	1111	10	0.0120	3699
SMPNPEGRYTF	281	11	0 0180	3700
SWLGLRSL	451	8	-0.0003	3701
SWLGLRSLREL	451	11	0.0036	3702
SYGVTVWEL	907	9	0.1200	3703
SYLEDVRL	834	8	0.0059	3704
SYMPIWKF	609	8	0.3200	3705
TFGAKPYDGI	917	10	0.0002	3706
TMRRLLQETEL	686	11	-0.0003	3707
TYLPTNASL	63	9	0.0380	3708
TYLPTNASLSF	63	11	8.9000	3709
VFETLEEI	399	8	-0.0003	3710
VFQNLQVI	424	8	-0.0003	3711
VWSYGVTVW	905	9	0 0800	3712
VWSYGVTVWEL	905	11	0.0920	3713
VYMIMVKCW	951	9	0.1600	3714
VYMIMVKCWMI	951	11	1.8000	3715
WMALESIL	888	8	-0.0003	3716
WMIDSECRPRF	959	11	0.0011	3717
YMIMVKCW	952	8	0.0009	3718
YMIMVKCWMI	952	10	0.0019	3719

Table XIX

HER2/NEU DR Super Motif Peptides with Binding Data

Core Sequence	Exemplary Sequence	Position	DR1	DR2wβ1	DR2w2β2	DR3	DR4w4	DR4w15	DR5w11	DR5w12	SEQ ID NO.
											3720
YNYLSTDVG	ACPYNYLSTDVGSCT	298									3721
VLRENTSPK	AIKVLRENTSPKANK	751				0.0075					3722
LQSLPTHDP	AKGLQSLPTHDPSPL	1095									3723
YDGIPAREI	AKPYDGIPAREIPDL	920									3724
LDIDETEYH	ARLLDIDETEYHADG	867	0 0001	-0 0006	-0 0007	0.3100	-0.0055		-0.0008		3725
VLVKSPNHV	ARNVLVKSPNHVKIT	848									3726
LTSIISAVV	ASPLTSIISAVVGIL	648	0.0890	0 0950	0 0037	0.0010	-0 0025		-0.0005		3727
LTLQGLGIS	AYSLTLQGLGISWLG	440									3728
MAGVGSPYV	AYVMAGVGSPYVSRL	771									3729
IFGSLAFLP	CKKIFGSLAFLPESF	367	0.2400	0.0070	0.0016	0.0010	-0 0025		-0.0005		3730
FNHSGICEL	CLHFNHSGICELHCP	255									3731
IAKGMSYLE	CMQIAKGMSYLEDVR	826									3732
LVTYNTDTF	CPALVTYNTDTFESM	268									3733
LTRTVCAGG	CQSLTRTVCAGGCAR	212									3734
LDDKGCPAE	CVDLDDKGCPAEQRA	634									3735
LGMEHLREV	CYGLGMEHLREVRAV	342				0 0083					3736
YVMAGVGSP	DEAYVMAGVGSPYVS	769	0.0500	0.0029	0 0240	0.0010	0.2300		0.0027		3737
VGEGLACHQ	DECVGEGLACHQLCA	502									3738
LGMGAAKGL	DGDLGMGAAKGLQSL	1087									3739
VAPLTCSPQ	DGYVAPLTCSPQPEY	1125									3740
LGLEPSEEE	DLTLGLEPSEEEAPR	1058				-0.0025					3741
LRLPASPET	DMKLRLPASPETHLD	30	0.0010				-0.0025				3742
FCVARCPSG	DPPFCVARCPSGVKP	592									3743
FYRSLLEDD	DSTFYRSLLEDDDMG	1001									3744
LVHRDLAAR	DVRLVHRDLAARNVL	838									3745
MIMVKCWMI	DVYMIMVKCWMIDSE	950	0.0280	0.0047	0.0042	0.0010	0.0570		0.0220		3746
VLQGLPREY	ECRVLQGLPREYVNA	543									3747
YALAVLDNG	EDNYALAVLDNGDPL	109									3748
LPAARPAGA	EGPLPAARPAGATLE	1154									3749
YTFGASCVT	EGRYTFGASCVTACP	286									3750
YLPTNASLS	ELTYLPTNASLSFLQ	61									3751
LRRRFTHQS	ESILRRRFTHQSDVW	892									3752
LRKVKVLGS	ETELRKVKVLGSGAF	717	0.0160	0.0019	0 0052	0.0045	0.0350		0.0061		3753
LVEPLTPSG	ETELVEPLTPSGAMP	693	0 0060				-0 0025				3754
LVSEFSRMA	FRELVSEFSRMARDP	969				0.0710					3755
IQNEDLGPA	FVVIQNEDLGPASPL	986				-0 0025					3756
LERPKTLSP	GATLERPKTLSPGKN	1164									3757
VVQGNLELT	GCQVVQGNLELTYLP	52									3758
LNNTTPVTG	GDPLNNTTPVTGASP	120									3759
LACHQLCAR	GEGLACHQLCARGHC	506									3760
VKIPVAIKV	GENVKIPVAIKVLRE	743	0.0630	0.0047	0.0034	0.0098	-0.0032		-0.0005		3761
LPQPPICTI	GERLPQPPICTIDVY	938	-0.0005				-0.0032				3762
VPIKWMALE	GGKVPIKWMALESIL	881									3763
LIQRNPQLC	GGVLIQRNPQLCYQD	151									3764
WGPGPTQCV	GHCWGPGPTQCVNCS	518									3765
WLGLRSLRE	GISWLGLRSLRELGS	449									3766
LIHHNTHLC	GLALIHHNTHLCFVH	464									3767
ISWLGLRSL	GLGISWLGLRSLREL	447									3768
LALLPPGAA	GLLLALLPPGAASTQ	10									3769
VFDGDLGMG	GSDVFDGDLGMGAAK	1082									

Table XIX

HER2/NEU DR Super Motif Peptides with Binding Data

Core Sequence	Exemplary Sequence	DR6w19	DR7	DR8w2	DR9	DRw53	SEQ ID NO.
YNYLSTDVG	ACPYNYLSTDVGSCT						3720
VLRENTSPK	AIKVLRENTSPKANK						3721
LQSLPTHDP	AKGLQSLPTHDPSPL						3722
YDGIPAREI	AKPYDGIPAREIPDL						3723
LDIDETEYH	ARLLDIDETEYHADG	-0.0001	-0.0017	-0.0009			3724
VLVKSPNHV	ARNVLVKSPNHVKIT						3725
LTSHSAVV	ASPLTSHSAVVGIL	0.0480	0.0350	-0.0004			3726
LTLQGLGIS	AYSLTLQGLGISWLG						3727
MAGVGSPYV	AYVMAGVGSPYVSRL						3728
IFGSLAFLP	CKKIFGSLAFLPESF	0.0034	0.0270	-0.0004			3729
FNHSGICEL	CLHFNHSGICELHCP						3730
IAKGMSYLE	CMQIAKGMSYLEDVR						3731
LVTYNTDTF	CPALVTYNTDTFESM						3732
LTRTVCAGG	CQSLTRTVCAGGCAR						3733
LDDKGCPAE	CVDLDDKGCPAEQRA						3734
LGMEHLREV	CYGLGMEHLREVRAV						3735
YVMAGVGSP	DEAYVMAGVGSPYVS	0.0020	0.2000	0.0570			3736
VGEGLACHQ	DECVGEGLACHQLCA						3737
LGMGAAKGL	DGDLGMGAAKGLQSL						3738
VAPLTCSPQ	DGYVAPLTCSPQPEY						3739
LGLEPSEEE	DLTLGLEPSEEEAPR						3740
LRLPASPET	DMKLRLPASPETHLD		-0.0013				3741
FCVARCPSG	DPPFCVARCPSGVKP						3742
FYRSLLEDD	DSTFYRSLLEDDDMG						3743
LVHRDLAAR	DVRLVHRDLAARNVL						3744
MIMVKCWMI	DVYMIMVKCWMIDSE	-0.0003	0.1300	0.0450			3745
VLQGLPREY	ECRVLQGLPREYVNA						3746
YALAVLDNG	EDNYALAVLDNGDPL						3747
LPAARPAGA	EGPLPAARPAGATLE						3748
YTFGASCVT	EGRYTFGASCVTACP						3749
YLPTNASLS	ELTYLPTNASLSFLQ						3750
LRRRFTHQS	ESILRRRFTHQSDVW						3751
LRKVKVLGS	ETELRKVKVLGSGAF	0.0014	0.0380	0.0250			3752
LVEPLTPSG	ETELVEPLTPSGAMP		-0.0013				3753
LVSEFSRMA	FRELVSEFSRMARDP						3754
IQNEDLGPA	FVVIQNEDLGPASPL						3755
LERPKTLSP	GATLERPKTLSPGKN						3756
VVQGNLELT	GCQVVQGNLELTYLP						3757
LNNTTPVTG	GDPLNNTTPVTGASP						3758
LACHQLCAR	GEGLACHQLCARGHC						3759
VKIPVAIKV	GENVKIPVAIKVLRE	0.0004	0.0310	0.0010			3760
LPQPPICTI	GERLPQPPICTIDVY		-0.0011				3761
VPIKWMALE	GGKVPIKWMALESIL						3762
LIQRNPQLC	GGVLIQRNPQLCYQD						3763
WGPGPTQCV	GHCWGPGPTQCVNCS						3764
WLGLRSLRE	GISWLGLRSLRELGS						3765
LIHHNTHLC	GLALIHHNTHLCFVH						3766
ISWLGLRSL	GLGISWLGLRSLREL						3767
LALLPPGAA	GLLLALLPPGAASTQ						3768
VFDGDLGMG	GSDVFDGDLGMGAAK						3769

Table XIX:

HER2/NEU DR Super Motif Peptides with Binding Data

Core Sequence	Exemplary Sequence	Position	DR1	DR2wß1	DR2w2ß2	DR3	DR4w4	DR4w15	DR5w11	DR5w12	SEQ ID NO.
YVSRLLGIC	GSPYVSRLLGICLTS	778									3770
MKLRLPASP	GTDMKLRLPASPETH	28	0.0010				-0 0025				3771
YKGIWIPDG	GTVYKGIWIPDGENV	732									3772
VWELMTFGA	GVTVWELMTFGAKPY	909	1.4000				0.0330				3773
YISAWPDSL	GYLYISAWPDSLPDL	408									3774
FVHTVPWDQ	HLCFVHTVPWDQLFR	473									3775
VRQVPLQRL	HNQVRQVPLQRLRIV	88									3776
LAARNVLVK	HRDLAARNVLVKSPN	843									3777
ICELHCPAL	HSGICELHCPALVTY	260									3778
ITDFGLARL	HVKITDFGLARLLDI	858									3779
LHCPALVTY	ICELHCPALVTYNTD	263									3780
IDVYMIMVK	ICTIDVYMIMVKCWM	946									3781
LRENTSPKA	IKVLRENTSPKANKE	752	-0.0005				-0.0032				3782
MALESILRR	IKWMALESILRRRFT	886	0.9500				0.0400				3783
VVVLGVVFG	ILLVVVLGVVFGILI	661									3784
VQGYVLIAH	IQEVQGYVLIAHNQV	77									3785
YTMRRLLQE	IRKYTMRRLLQETEL	682									3786
VVGILLVVV	ISAVVGILLVVVLGV	655									3787
WPDSLPDLS	ISAWPDSLPDLSVFQ	412									3788
LGLRSLREL	ISWLGLRSLRELGSG	450									3789
FGLARLLDI	ITDFGLARLLDIDET	861	0.0048				-0.0032				3790
YLYISAWPD	ITGYLYISAWPDSLP	406									3791
MIDSECRPR	KCWMIDSECRPRFRE	957									3792
FAFGGAVEN	KDVFAFGGAVENPEY	1182									3793
LDEAYVMAG	KEILDEAYVMAGVGS	765	0.0036				0.0073				3794
LPTDCCHEQ	KGPLPTDCCHEQCAA	228				-0.0027					3795
VAIKVLREN	KIPVAIKVLRENTSP	747									3796
LSYMPIWKF	KPDLSYMPIWKFPDE	605	0.0330				-0.0025				3797
VLGSGAFGT	KVKVLGSGAFGTVYK	722									3798
IKWMALESI	KVPIKWMALESILRR	883	2 2000	2.7000	2 1000	0.0620	0.0690		0.0073		3799
LCRWGLLLA	LAALCRWGLLLALLP	3									3800
LHFNHSGIC	LACLHFNHSGICELH	253									3801
LPPGAASTQ	LALLPPGAASTQVCT	13									3802
LDNGDPLNN	LAVLDNGDPLNNTTP	114									3803
WGLLLALLP	LCRWGLLLALLPPGA	6	0.0940				-0.0025				3804
VFGILIKRR	LGVVFGILIKRRQQK	667									3805
LLPPGAAST	LLALLPPGAASTQVC	12									3806
ICLTSTVQL	LLGICLTSTVQLVTQ	785									3807
WCMQIAKGM	LLNWCMQIAKGMSYL	822	0.8400	0.0057	1.2000	0.0093	0.0011		0.4000		3808
VVLGVVFGI	LLVVVLGVVFGILIK	662	-0.0008				-0.0025				3809
LGISWLGLR	LQGLGISWLGLRSLR	445									3810
LPREYVNAR	LQGLPREYVNARHCL	547				-0.0027					3811
YSEDPTVPL	LQRYSEDPTVPLPSE	1109				0.0270					3812
LPTHDPSPL	LQSLPTHDPSPLQRY	1098									3813
IRGRILHNG	LQVIRGRILIINGAYS	428									3814
LGSGLALIH	LRELGSGLALIHHNT	458	0.0310				-0.0025				3815
LQLRSLTEI	LRELQLRSLTEILKG	137									3816
VRAVTSANI	LREVRAVTSANIQEF	350									3817
VRGTQLFED	LRIVRGTQLFEDNYA	99									3818
VKVLGSGAF	LRKVKVLGSGAFGTV	720									3819

TableXIX

HER2/NEU DR Super Motif Peptides with Binding Data

Core Sequence	Exemplary Sequence	DR6w19	DR7	DR8w2	DR9	DRw53	SEQ ID NO.
YVSRLLGIC	GSPYVSRLLGICLTS						3770
MKLRLPASP	GTDMKLRLPASPETH		-0 0013				3771
YKGIWIPDG	GTVYKGIWIPDGENV						3772
VWELMTFGA	GVTVWELMTFGAKPY		0.0170				3773
YISAWPDSL	GYLYISAWPDSLPDL						3774
FVHTVPWDQ	HLCFVHTVPWDQLFR						3775
VRQVPLQRL	HNQVRQVPLQRLRIV						3776
LAARNVLVK	HRDLAARNVLVKSPN						3777
ICELHCPAL	HSGICELHCPALVTY						3778
ITDFGLARL	HVKITDFGLARLLDI						3779
LHCPALVTY	ICELHCPALVTYNTD						3780
IDVYMIMVK	ICTIDVYMIMVKCWM						3781
LRENTSPKA	IKVLRENTSPKANKE		-0.0011				3782
MALESILRR	IKWMALESILRRRFT		0.0040				3783
VVVLGVVFG	ILLVVVLGVVFGILI						3784
VQGYVLIAH	IQEVQGYVLIAHNQV						3785
YTMRRLLQE	IRKYTMRRLLQETEL						3786
VVGILLVVV	ISAVVGILLVVVLGV						3787
WPDSLPDLS	ISAWPDSLPDLSVFQ						3788
LGLRSLREL	ISWLGLRSLRELGSG						3789
FGLARLLDI	ITDFGLARLLDIDET		-0.0011				3790
YLYISAWPD	ITGYLYISAWPDSLP						3791
MIDSECRPR	KCWMIDSECRPRFRE						3792
FAFGGAVEN	KDVFAFGGAVENPEY						3793
LDEAYVMAG	KEILDEAYVMAGVGS		-0 0011				3794
LPTDCCHEQ	KGPLPTDCCHEQCAA						3795
VAIKVLREN	KIPVAIKVLRENTSP						3796
LSYMPIWKF	KPDLSYMPIWKFPDE		0 0029				3797
VLGSGAFGT	KVKVLGSGAFGTVYK						3798
IKWMALESI	KVPIKWMALESILRR	0.0031	0.0190	0.0079			3799
LCRWGLLLA	LAALCRWGLLLALLP						3800
LHFNHSGIC	LACLHFNHSGICELH						3801
LPPGAASTQ	LALLPPGAASTQVCT						3802
LDNGDPLNN	LAVLDNGDPLNNTTP						3803
WGLLLALLP	LCRWGLLLALLPPGA		0.0021				3804
VFGILIKRR	LGVVFGILIKRRQQK						3805
LLPPGAAST	LLALLPPGAASTQVC						3806
ICLTSTVQL	LLGICLTSTVQLVTQ						3807
WCMQIAKGM	LLNWCMQIAKGMSYL	0.0390	0 1200	0.4100			3808
VVLGVVFGI	LLVVVLGVVFGILIK		0 0019				3809
LGISWLGLR	LQGLGISWLGLRSLR						3810
LPREYVNAR	LQGLPREYVNARHCL						3811
YSEDPTVPL	LQRYSEDPTVPLPSE						3812
LPTHDPSPL	LQSLPTHDPSPLQRY						3813
IRGRILHNG	LQVIRGRILHNGAYS						3814
LGSGLALIH	LRELGSGLALIHHNT		-0.0013				3815
LQLRSLTEI	LRELQLRSLTEILKG						3816
VRAVTSANI	LREVRAVTSANIQEF						3817
VRGTQLFED	LRIVRGTQLFEDNYA						3818
VKVLGSGAF	LRKVKVLGSGAFGTV						3819

Table XIX.

HER2/NEU DR Super Motif Peptides with Binding Data

Core Sequence	Exemplary Sequence	Position	DR1	DR2wβ1	DR2w2β2	DR3	DR4w4	DR4w15	DR5w11	DR5w12	SEQ ID NO.
LRELGSGLA	LRSLRELGSGLALIH	455									3820
FQNLQVIRG	LSVFQNLQVIRGRIL	422	0.1800	0.0280	0 0740	0.0010	0.0670		0.0100		3821
ILKGGVLIQ	LTEILKGGVLIQRNP	145									3822
IDTNRSRAC	LTLIDTNRSRACHPC	181									3823
IISAVVGIL	LTSIISAVVGILLVV	651	0.1900				-0.0025				3824
LPTNASLSF	LTYLPTNASLSFLQD	62	0.4900	0.0100	0.0560	0.0150	0.3300		0.0041		3825
WDQDPPERG	LYYWDQDPPERGAPP	1220									3826
VGSPYVSRL	MAGVGSPYVSRLLGI	774									3827
LREVRAVTS	MEHLREVRAVTSANI	347									3828
VKCWMIDSE	MIMVKCWMIDSECRP	953									3829
LKETELRKV	MRILKETELRKVKVL	712									3830
LEDVRLVHR	MSYLEDVRLVHRDLA	833									3831
LGPASPLDS	NEDLGPASPLDSTFY	991									3832
VTCFGPEAD	NGSVTCFGPEADQCV	571									3833
VKDVFAFGG	NGVVKDVFAFGGAVE	1178									3834
LTYLPTNAS	NLELTYLPTNASLSF	59	0.4700	0.0280	0.0090	0.0010	0.3800		0.0050		3835
VIRGRILHN	NLQVIRGRILHNGAY	427									3836
YWDQDPPER	NLYYWDQDPPERGAP	1219									3837
LALTLIDTN	NNQLALTLIDTNRSR	176									3838
LCYQDTILW	NPQLCYQDTILWKDI	158									3839
LCFVHTVPW	NTHLCFVHTVPWDQL	471									3840
INCTHSCVD	PCPINCTHSCVDLDD	625									3841
LPDLSVFQN	PDSLPDLSVFQNLQV	416									3842
LQVFETLEE	PEQLQVFETLEEITG	394									3843
FDGDPASNT	PESFDGDPASNTAPL	378				-0.0027					3844
VNQPDVRPQ	PEYVNQPDVRPQPPS	1137									3845
VARCPSGVK	PFCVARCPSGVKPDL	594									3846
LRELQLRSL	PGGLRELQLRSLTEI	134									3847
WMALESILR	PIKWMALESILRRRF	885	0.7900				0.0350				3848
VKPDLSYMP	PSGVKPDLSYMPIWK	601				-0.0027					3849
FKGTPTAEN	PSTFKGTPTAENPEY	1234	-0.0005				-0.0032				3850
YLSTDVGSC	PYNYLSTDVGSCTLV	300									3851
ILWKDIFHK	QDTILWKDIFHKNNQ	164									3852
VEECRVLQG	QECVEECRVLQGLPR	538									3853
FCPDPAPGA	QGFFCPDPAPGAGGM	1028	-0.0005				0.0230				3854
LELTYLPTN	QGNLELTYLPTNASL	57									3855
LTLIDTNRS	QLALTLIDTNRSRAC	178									3856
YQDTILWKD	QLCYQDTILWKDIFH	160									3857
VRPQPPSPR	QPDVRPQPPSPREGP	1142	0 0007				-0 0032				3858
ICTIDVYMI	QPPICTIDVYMIMVK	943	0.0670	0.0540	0 0027	0.0976	0.0060		0.0046		3859
FFCPDPAPG	QQGFFCPDPAPGAGG	1027									3860
IRKYTMRRL	QQKIRKYTMRRLLQE	679									3861
VWSYGVTVW	QSDVWSYGVTVWELM	902									3862
LQRLRIVRG	QVPLQRLRIVRGTQL	93									3863
VNARHCLPC	REYVNARHCLPCHPE	552									3864
ILHNGAYSL	RGRILHNGAYSLTLQ	432									3865
LGSQDLLNW	RGRLGSQDLLNWCMQ	814									3866
YQGCQVVQG	RHLYQGCQVVQGNLE	47									3867
FRELVSEFS	RPRFRELVSEFSRMA	966									3868
LQETELVEP	RRLLQETELVEPLTP	688									3869

Table XIX.

HER2/NEU DR Super Motif Peptides with Binding Data

Core Sequence	Exemplary Sequence	DR6w19	DR7	DR8w2	DR9	DRw53	SEQ ID NO.
LRELGSGLA	LRSLRELGSGLALIH						3820
FQNLQVIRG	LSVFQNLQVIRGRIL	0.0057	0.2900	0.0330			3821
ILKGGVLIQ	LTEILKGGVLIQRNP						3822
IDTNRSRAC	LTLIDTNRSRACHPC						3823
IISAVVGIL	LTSIISAVVGILLVV		0.0049				3824
LPTNASLSF	LTYLPTNASLSFLQD	0 0280	0 3200	0.0054			3825
WDQDPPERG	LYYWDQDPPERGAPP						3826
VGSPYVSRL	MAGVGSPYVSRLLGI						3827
LREVRAVTS	MEHILREVRAVTSANI						3828
VKCWMIDSE	MIMVKCWMIDSECRP						3829
LKETELRKV	MRILKETELRKVKVL						3830
LEDVRLVHR	MSYLEDVRLVHRDLA						3831
LGPASPLDS	NEDLGPASPLDSTFY						3832
VTCFGPEAD	NGSVTCFGPEADQCV						3833
VKDVFAFGG	NGVVKDVFAFGGAVE						3834
LTYLPTNAS	NLELTYLPTNASLSF	0.0017	0.0680	0.0220			3835
VIRGRILHN	NLQVIRGRILHNGAY						3836
YWDQDPPER	NLYYWDQDPPERGAP						3837
LALTLIDTN	NNQLALTLIDTNRSR						3838
LCYQDTILW	NPQLCYQDTILWKDI						3839
LCFVHTVPW	NTHLCFVHTVPWDQL						3840
INCTHSCVD	PCPINCTHSCVDLDD						3841
LPDLSVFQN	PDSLPDLSVFQNLQV						3842
LQVFETLEE	PEQLQVFETLEEITG						3843
FDGDPASNT	PESFDGDPASNTAPL						3844
VNQPDVRPQ	PEYVNQPDVRPQPPS						3845
VARCPSGVK	PFCVARCPSGVKPDL						3846
LRELQLRSL	PGGLRELQLRSLTEI						3847
WMALESILR	PIKWMALESILRRRF		0 0078				3848
VKPDLSYMP	PSGVKPDLSYMPIWK						3849
FKGTPTAEN	PSTFKGTPTAENPEY		-0.0011				3850
YLSTDVGSC	PYNYLSTDVGSCTLV						3851
ILWKDIFHK	QDTILWKDIFHKNNQ						3852
VEECRVLQG	QECVEECRVLQGLPR						3853
FCPDPAPGA	QGFFCPDPAPGAGGM		-0.0011				3854
LELTYLPTN	QGNLELTYLPTNASL						3855
LTLIDTNRS	QLALTLIDTNRSRAC						3856
YQDTILWKD	QLCYQDTILWKDIFH						3857
VRPQPPSPR	QPDVRPQPPSPREGP		-0.0011				3858
ICTIDVYMI	QPPICTIDVYMIMVK	0 0013	0.1000	0.0051			3859
FFCPDPAPG	QQGFFCPDPAPGAGG						3860
IRKYTMRRL	QQKIRKYTMRRLLQE						3861
VWSYGVTVW	QSDVWSYGVTVWELM						3862
LQRLRIVRG	QVPLQRLRIVRGTQL						3863
VNARHCLPC	REYVNARHCLPCHPE						3864
ILHNGAYSL	RGRILHNGAYSLTLQ						3865
LGSQDLLNW	RGRLGSQDLLNWCMQ						3866
YQGCQVVQG	RHLYQGCQVVQGNLE						3867
FRELVSEFS	RPRFRELVSEFSRMA						3868
LQETELVEP	RRLLQETELVEPLTP						3869

Table XIX

HER2/NEU DR Super Motif Peptides with Binding Data

Core Sequence	Exemplary Sequence	Position	DR1	DR2wß1	DR2w2ß2	DR3	DR4w4	DR4w15	DR5w11	DR5w12	SEQ ID NO.
LEDDDMGDL	RSLLEDDDMGDLVDA	1006				0.0080					3870
LLLALLPPG	RWGLLLALLPPGAAS	8	12 0000	0 1300	0.0270	0 0010	0 2800		0.0710		3871
FGASCVTAC	RYTFGASCVTACPYN	288									3872
VGILLVVVL	SAVVGILLVVVLGVV	656									3873
WSYGVTVWE	SDVWSYGVTVWELMT	903									3874
LQGLGISWL	SLTLQGLGISWLGLR	442									3875
LLNWCMQIA	SQDLLNWCMQIAKGM	819									3876
LRGQECVEE	SQFLRGQECVEECRV	532									3877
LGICLTSTV	SRLLGICLTSTVQLV	783	0 3500	0.0220	-0 0007	0.0062	0.1200		0.0140		3878
VGSCTLVCP	STDVGSCTLVCPLHN	305									3879
VTVWELMTF	SYGVTVWELMTFGAK	907									3880
LQPEQLQVF	TAPLQPEQLQVFETL	389				0 0023					3881
YVAPLTCSP	TDGYVAPLTCSPQPE	1124	-0.0005				-0.0032				3882
LKGGVLIQR	TEILKGGVLIQRNPQ	146									3883
VEPLTPSGA	TELVEPLTPSGAMPN	694									3884
VYMIMVKCW	TIDVYMIMVKCWMID	948									3885
FEDNYALAV	TQLFEDNYALAVLDN	105	0.0530				-0.0025				3886
MPYGCLLDH	TQLMPYGCLLDHVRE	798									3887
VCAGGCARC	TRTVCAGGCARCKGP	216									3888
VTGASPGGL	TTPVTGASPGGLREL	126									3889
LVTQLMPYG	TVQLVTQLMPYGCLL	793	0.2300	0.7500	0.0009	0.0010	0.0460		-0.0005		3890
LHNQEVTAE	VCPLHNQEVTAEDGT	314	-0.0004				-0.0025				3891
LTPSGAMPN	VEPLTPSGAMPNQAQ	697	-0.0008				-0.0025				3892
LLVVVLGVV	VGILLVVVLGVVFGI	659									3893
VPWDQLFRN	VHTVPWDQLFRNPHQ	477				0.0220					3894
VVFGILIKR	VLGVVFGILIKRRQQ	666	0.0700	0.0110	0.0620	0.0021	0 0029		0.4700		3895
VTQLMPYGC	VQLVTQLMPYGCLLD	794									3896
VTSANIQEF	VRAVTSANIQEFAGC	353									3897
VHRDLAARN	VRLVHRDLAARNVLV	839	0.0340	0.0064	0 0033	0.3400	0.0150		0.2700		3898
VPLQRLRIV	VRQVPLQRLRIVRGT	91									3899
LLGICLTST	VSRLLGICLTSTVQL	782									3900
LMPYGCLLD	VTQLMPYGCLLDHVR	797									3901
ILLVVVLGV	VVGILLVVVLGVVFG	658	-0.0004				-0.0025				3902
LMTFGAKPY	VWELMTFGAKPYDGI	912	0 0870	0.0990	0 1000	0.0010	0.0550		0.0054		3903
LLALLPPGA	WGLLLALLPPGAAST	9	5.1000	0.2100	0 0110	0 0013	1.3000		0.2500		3904
IPAREIPDL	YDGIPAREIPDLLEK	923									3905
MVKCWMIDS	YMIMVKCWMIDSECR	952									3906
IAHNQVRQV	YVLIAHNQVRQVPLQ	83									3907

TableXIX

HER2/NEU DR Super Motif Peptides with Binding Data

Core Sequence	Exemplary Sequence	DR6w19	DR7	DR8w2	DR9	DRw53	SEQ ID NO.
							3870
LEDDDMGDL	RSLLEDDDMGDLVDA						3871
LLLALLPPG	RWGLLLALLPPGAAS	-0.0003	-0.0013	0.1200			3872
FGASCVTAC	RYTFGASCVTACPYN						3873
VGILLVVVL	SAVVGILLVVVLGVV						3874
WSYGVTVWE	SDVWSYGVTVWELMT						3875
LQGLGISWL	SLTLQGLGISWLGLR						3876
LLNWCMQIA	SQDLLNWCMQIAKGM						3877
LRGQECVEE	SQFLRGQECVEECRV						3878
LGICLTSTV	SRLLGICLTSTVQLV	0.3400	0.5600	0.0009			3879
VGSCTLVCP	STDVGSCTLVCPLHN						3880
VTVWELMTF	SYGVTVWELMTFGAK						3881
LQPEQLQVF	TAPLQPEQLQVFETL						3882
YVAPLTCSP	TDGYVAPLTCSPQPE		-0 0011				3883
LKGGVLIQR	TEILKGGVLIQRNPQ						3884
VEPLTPSGA	TELVEPLTPSGAMPN						3885
VYMIMVKCW	TIDVYMIMVKCWMID						3886
FEDNYALAV	TQLFEDNYALAVLDN		0.0160				3887
MPYGCLLDH	TQLMPYGCLLDHVRE						3888
VCAGGCARC	TRTVCAGGCARCKGP						3889
VTGASPGGL	TTPVTGASPGGLREL						3890
LVTQLMPYG	TVQLVTQLMPYGCLL	0.0031	0 0100	0.0069			3891
LHNQEVTAE	VCPLHNQEVTAEDGT		-0.0013				3892
LTPSGAMPN	VEPLTPSGAMPNQAQ		-0.0011				3893
LLVVVLGVV	VGILLVVVLGVVFGI						3894
VPWDQLFRN	VHTVPWDQLFRNPHQ						3895
VVFGILIKR	VLGVVFGILIKRRQQ	0.0150	0.0320	0 6400			3896
VTQLMPYGC	VQLVTQLMPYGCLLD						3897
VTSANIQEF	VRAVTSANIQEFAGC						3898
VHRDLAARN	VRLVHRDLAARNVLV	0 0430	0.0230	0.1000			3899
VPLQRLRIV	VRQVPLQRLRIVRGT						3900
LLGICLTST	VSRLLGICLTSTVQL						3901
LMPYGCLLD	VTQLMPYGCLLDHVR						3902
ILLVVVLGV	VVGILLVVVLGVVFG		-0.0013				3903
LMTFGAKPY	VWELMTFGAKPYDGI	0 0004	0.0370	0.0089			3904
LLALLPPGA	WGLLLALLPPGAAST	-0.0003	-0.0013	0.4500			3905
IPAREIPDL	YDGIPAREIPDLLEK						3906
MVKCWMIDS	YMIMVKCWMIDSECR						3907
IAHNQVRQV	YVLIAHNQVRQVPLQ						

Table XXa

HER2/NEU DR 3a Motif Peptides with Binding Data

Core Sequence	Exemplary Sequence	Position	DR1	DR2w2β1	DR2w2β2	DR3	DR4w4	DR4w15	DR5w11	DR5w12	SEQ ID NO.
VLRENTSPK	AIKVLRENTSPKANK	751				0.0075					3908
LDIDETEYH	ARLLDIDETEYHADG	867	0.0001	-0.0006	-0 0007	0.3100	-0.0055		-0.0008		3909
LGMEHLREV	CYGLGMEHLREVRAV	342				0.0083					3910
LGLEPSEEE	DLTLGLEPSEEEAPR	1058				-0.0025					3911
YYWDQDPPE	DNLYYWDQDPPERGA	1218				-0.0025					3912
LWKDIFHKN	DTILWKDIFHKNNQL	165				-0.0027					3913
YHADGGKVP	ETEYHADGGKVPIKW	874				-0.0027					3914
LVSEFSRMA	FRELVSEFSRMARDP	969				0.0710					3915
MARDPQRFV	FSRMARDPQRFVVIQ	976				0.1600					3916
IQNEDLGPA	FVVIQNEDLGPASPL	986				-0.0025					3917
VDAEEYLVP	GDLVDAEEYLVPQQG	1015				0.0250					3918
LFEDNYALA	GTQLFEDNYALAVLD	104				0.2200					3919
MALESILRR	IKWMALESILRRRFT	886	0.9500				0.0400				3920
FPDEEGACQ	IWKFPDEEGACQPCP	613				-0 0027					3921
LPTDCCHEQ	KGPLPTDCCHEQCAA	228				-0.0027					3922
VVKDVFAFG	KNGVVKDVFAFGGAV	1177				-0.0025					3923
LPREYVNAR	LQGLPREYVNARHCL	547				-0 0027					3924
YSEDPTVPL	LQRYSEDPTVPLPSE	1109				0.0270					3925
YNTDTFESM	LVTYNTDTFESMPNP	271				-0.0027					3926
LLQETELVE	MRRLLQETELVEPLT	687				-0.0027					3927
ILDEAYVMA	NKEILDEAYVMAGVG	764				0.0047					3928
VTAEDGTQR	NQEVTAEDGTQRCEK	319				-0 0027					3929
FDGDPASNT	PESFDGDPASNTAPL	378				-0.0027					3930
VKPDLSYMP	PSGVKPDLSYMPIWK	601				-0.0027					3931
FCPDPAPGA	QGFFCPDPAPGAGGM	1028	-0.0005				0.0230				3932
ILKETELRK	QMRILKETELRKVKV	711	0.0419	0.0150	0.5900	0.3200	-0.0055		0.0041		3933
LEDDDMGDL	RSLLEDDDMGDLVDA	1006				0.0080					3934
FDGDLGMGA	SDVFDGDLGMGAAKG	1083				-0.0025					3935
FLPESFDGD	SLAFLPESFDGDPAS	373				-0.0027					3936
FLQDIQEVQ	SLSFLQDIQEVQGYV	70				0.0520					3937
LQPEQLQVF	TAPLQPEQLQVFETL	389				0.0023					3938
LPSETDGYV	TVPLPSETDGYVAPL	1117				-0.0025					3939
VPWDQLFRN	VHTVPWDQLFRNPHQ	477				0.0220					3940
VHRDLAARN	VRLVHRDLAARNVLV	839	0.0340	0.0064	0.0033	0.3400	0.0150		0.2700		3941
FGPEADQCV	VTCFGPEADQCVACA	574				-0.0027					3942
LSTDVGSCT	YNYLSTDVGSCTLVC	301				0.0059					3943
LLEDDDMGD	YRSLLEDDDMGDLVD	1005				0.0630					3944

Table XXa

HER2/NEU DR 3a Motif Peptides with Binding Data

Core Sequence	Exemplary Sequence	DR6w19	DR7	DR8w2	DR9	DRw53	SEQ ID NO.
VLRENTSPK	AIKVLRENTSPKANK						3908
LDIDETEYH	ARLLDIDETEYHADG	-0.0001	-0.0017	-0.0009			3909
LGMEHLREV	CYGLGMEHLREVRAV						3910
LGLEPSEEE	DLTLGLEPSEEEAPR						3911
YYWDQDPPE	DNLYYWDQDPPERGA						3912
LWKDIFHKN	DTILWKDIFHKNNQL						3913
YHADGGKVP	ETEYHADGGKVPIKW						3914
LVSEFSRMA	FRELVSEFSRMARDP						3915
MARDPQRFV	FSRMARDPQRFVVIQ						3916
IQNEDLGPA	FVVIQNEDLGPASPL						3917
VDAEEYLVP	GDLVDAEEYLVPQQG						3918
LFEDNYALA	GTQLFEDNYALAVLD						3919
MALESILRR	IKWMALESILRRRFT		0.0040				3920
FPDEEGACQ	IWKFPDEEGACQPCP						3921
LPTDCCHEQ	KGPLPTDCCHEQCAA						3922
VVKDVFAFG	KNGVVKDVFAFGGAV						3923
LPREYVNAR	LQGLPREYVNARHCL						3924
YSEDPTVPL	LQRYSEDPTVPLPSE						3925
YNTDTFESM	LVTYNTDTFESMPNP						3926
LLQETELVE	MRRLLQETELVEPLT						3927
ILDEAYVMA	NKEILDEAYVMAGVG						3928
VTAEDGTQR	NQEVTAEDGTQRCEK						3929
FDGDPASNT	PESFDGDPASNTAPL						3930
VKPDLSYMP	PSGVKPDLSYMPIWK						3931
FCPDPAPGA	QGFFCPDPAPGAGGM		-0.0011				3932
ILKETELRK	QMRILKETELRKVKV	0.0008	0.0130	0.0064			3933
LEDDDMGDL	RSLLEDDDMGDLVDA						3934
FDGDLGMGA	SDVFDGDLGMGAAKG						3935
FLPESFDGD	SLAFLPESFDGDPAS						3936
FLQDIQEVQ	SLSFLQDIQEVQGYV						3937
LQPEQLQVF	TAPLQPEQLQVFETL						3938
LPSETDGYV	TVPLPSETDGYVAPL						3939
VPWDQLFRN	VHTVPWDQLFRNPHQ						3940
VHRDLAARN	VRLVHRDLAARNVLV	0.0430	0.0230	0.1000			3941
FGPEADQCV	VTCFGPEADQCVACA						3942
LSTDVGSCT	YNYLSTDVGSCTLVC						3943
LLEDDDMGD	YRSLLEDDDMGDLVD						3944

Table XXb

HER2/NEU DR 3b Motif Peptides with Binding Data

Core Sequence	Exemplary Sequence	Position	DR1	DR2w2β1	DR2w2β2	DR3	DR4w4	DR4w15	DR5w11	DR5w12	SEQ ID NO.
						0.0350					3945
LIDTNRSRA	ALTLIDTNRSRACHP	180				0.4500					3946
IDSECRPRF	CWMIDSECRPRFREL	958	0.0036	-0.0006	0.0150	0.1800	-0.0055		-0.0008		3947
YLEDVRLVH	GMSYLEDVRLVHRDL	832				-0.0027					3948
VDLDDKGCP	HSCVDLDDKGCPAEQ	632				0.3100					3949
IHHNTHLCF	LALIHHNTHLCFVHT	465	0.0140	0.0990	0 0009	-0.0025	-0.0055		0.0025		3950
AAPQPHPPP	QGGAAPQPHPPPAFS	1200				-0.0027					3951
ASPETHLDM	RLPASPETHLDMLRH	34				0.0290					3952
AHNQVRQVP	VLIAHNQVRQVPLQR	84				0.9000					3953
LFRNPHQAL	WDQLFRNPHQALLHT	482	-0 0001	0.0015	-0 0007		-0.0055		-0.0008		

Table XXb

HER2/NEU DR 3b Motif Peptides with Binding Data

Core Sequence	Exemplary Sequence	DR6w19	DR7	DR8w2	DR9	DRw53	SEQ ID NO.
LIDTNRSRA	ALTLIDTNRSRACHP						3945
IDSECRPRF	CWMIDSECRPRFREL	-0.0001	-0.0014	0.0028			3946
YLEDVRLVH	GMSYLEDVRLVHRDL						3947
VDLDDKGCP	HSCVDLDDKGCPAEQ						3948
IHHNTHLCF	LALIHHNTHLCFVHT	0.7500	0.0200	0.0330			3949
AAPQPHPPP	QGGAAPQPHPPPAFS						3950
ASPETHLDM	RLPASPETHLDMLRH						3951
AHNQVRQVP	VLIAHNQVRQVPLQR						3952
LFRNPHQAL	WDQLFRNPHQALLHT	0.0410	-0.0017	-0.0009			3953

TABLE XXI. Population coverage with combined HLA Supertypes

HLA-SUPERTYPES	PHENOTYPIC FREQUENCY					
	Caucasian	North American Black	Japanese	Chinese	Hispanic	Average
a. Individual Supertypes						
A2	45.8	39.0	42.4	45.9	43.0	43.2
A3	37.5	42.1	45.8	52.7	43.1	44.2
B7	38.6	52.7	48.8	35.5	47.1	44.7
A1	47.1	16.1	21.8	14.7	26.3	25.2
A24	23.9	38.9	58.6	40.1	38.3	40.0
B44	43.0	21.2	42.9	39.1	39.0	37.0
B27	28.4	26.1	13.3	13.9	35.3	23.4
B62	12.6	4.8	36.5	25.4	11.1	18.1
B58	10.0	25.1	1.6	9.0	5.9	10.3
b. Combined Supertypes						
A2, A3, B7	83.0	86.1	87.5	88.4	86.3	86.2
A2, A3, B7, A24, B44, A1	99.5	98.1	100.0	99.5	99.4	99.3
A2, A3, B7, A24, B44, A1, B27, B62, B58	99.9	99.6	100.0	99.8	99.9	99.8

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Table XXII. A2 supermotif analog peptides

Source	AA	Sequence	A*0201 nM	A*0202 nM	A*0203 nM	A*0206 nM	A*6802 nM	No. A2 Alleles Crossbound
Her2/neu.5	9	ALCRWGLLL	100	--	278	--	--	2
Her2/neu.5B3V9	9	ALBRWGLLV	18	33	4.2	285	--	4
Her2/neu.5M2B3V9	9	AMBRWGLLV	36	473	16	726	--	3
Her2/neu.153	9	VLIQRNPQL	23	3909	3.3	1057	--	2
Her2/neu.153V9	9	VLIQRNPQV	55	768	135	385	--	3
Her2/neu.369	9	KIFGSLAFL	36	9.0	19	23	3333	4
Her2/neu.369V2V9	9	KVFGSLAFV	20	19.0	769	15	29	4
Her2/neu.369T2V9	9	KTFGSLAFV	35	13.0	1010	14	17	4
Her2/neu.369L2V9	9	KLFGSLAFV	5.8	7.5	19	17	1270	4
Her2/neu.653	9	SIISAVVGI	69	524	35	285	148	4
Her2/neu.653.L2V9	9	SLISAVVGV	7.1	10	16	20	110	5
Her2/neu.665	9	VVLGVVFGI	14	--	2500	430	2000	2
Her2/neu.665V2V9	9	VVLGVVFGV						
Her2/neu.665L2V9	9	VLLGVVFGV	2.4	17	14	6.0	8000	4
Her2/neu.952	10	YMIMVKCWMI	20	307	83	116	267	5
Her2/neu.952L2V10	10	YLIMVKCWMV	13	56	116	18	84	5
Her2/neu.952L2B7V10	10	YLIMVKBWMV	7.2	66	77	11	851	4

-- indicates binding affinity =10,000nM.

Table XXII A01A Analog Peptides

Peptide	AA	Sequence	Source	A*0101 nM
52.0013	8	VTACPYNY	Her2/neu.296	250
52.0118	11	ETHLDMLRHLY	Her2/neu.40	89.3
52.0121	11	ASCVTACPYNY	Her2/neu.293	131.6
52.0124	11	ETLEEITGYLY	Her2/neu.401	56.8
52.0125	11	EADQCVACAHY	Her2/neu.580	250
57.0016	9	HTDMLRHLY	Her2/neu.42.T2	1.9
57.0017	9	GTDLFEDNY	Her2/neu.104.D3	0.9
57.0018	9	ATCVTACPY	Her2/neu.293.T2	49
57.0019	9	ETDEEITGY	Her2/neu.401.D3	16.7
57.0022	9	VMDGVGSPY	Her2/neu.773.D3	39.7
57.0023	9	LTDIDETEY	Her2/neu.869.T2	5.7
57.0024	9	ATPLDSTFY	Her2/neu.997.T2	36.2
57.0025	9	LTDSPQPEY	Her2/neu.1131.D3	31.6
57.0027	9	FTPAFDNLY	Her2/neu.1213.T2	7.8
57.0028	9	SPDFDNLYY	Her2/neu.1214.D3	73.5
57.0107	10	GTDMKLRLPY	Her2/neu.28.Y10	50
57.0109	10	PTDCCHEQCY	Her2/neu.232.Y10	46.3
57.011	10	PTDCCHEQCA	Her2/neu.232	125
57.0111	10	ETMPNPEGRY	Her2/neu.280.T2	3.9
57.0112	10	TLDEITGYLY	Her2/neu.402.D3	3.4
57.0113	10	CTQIAKGMSY	Her2/neu.826.T2	19.2
57.0114	10	FTDQSDVWSY	Her2/neu.899.D3	0.6
57.0115	10	PADPLDSTFY	Her2/neu.996.D3	19.2
57.0116	10	MTDLVDAEEY	Her2/neu.1014.T2	2.3
57.0117	10	FTPAFDNLYY	Her2/neu.1213.T2	0.8
57.0118	10	GTDTAENPEY	Her2/neu.1239.D3	25.8
57.0129	11	PTDCCHEQCAY	Her2/neu.232.Y11	17.9
57.013	11	PTDCCHEQCAA	Her2/neu.232	58.1

Table XXIIB A03 Analog Peptides

Peptide	AA	Sequence	Source	A*0301 nM	A*1101 nM	A*3101 nM	A*3301 nM	A*6801 nM	A3 XRN
1371.34	10	IVKGGVLIQR	Her2/neu.148.V2	275	7500	72	126.1	28.6	4
1371.35	10	IVKGGVLIQK	Her2/neu.148.V2K10	26.2	101.7	450	6590.9	26.7	4
1371.36	10	TVLWKDIFHK	Her2/neu.166.V2	733.3	40	9000	5686.3	470.6	2
1371.37	10	TVLWKDIFHR	Her2/neu.166.V2R10	8461.5	285.7	600	76.3	42.1	3
1371.38	9	IVWKDIFHK	Her2/neu.167.V2	23.4	40	246.6	852.9	177.8	4
1371.39	9	IVWKDIFHR	Her2/neu.167.V2R9	142.9	285.7	6	16.1	15.4	5
1371.4	9	TVBAGGBAR	Her2/neu.218.B3B7	314.3	111.1	246.6	241.7	8	5
1371.41	9	TVBAGGBAK	Her2/neu.218.B3B7K9	23.9	28.6	45000	36250	7.3	3
1371.42	10	IVWLGLRSLR	Her2/neu.450.V2	234	1935.5	11.3	193.3	7.3	4
1371.43	10	IVWLGLRSLK	Her2/neu.450.V2K10	3.9	127.7	272.7	2071.4	11.6	4
1371.44	10	HVVPWDQLFR	Her2/neu.478.V2	7333.3	1333.3	391.3	193.3	3.6	3
1371.45	10	HVVPWDQLFK	Her2/neu.478.V2K10	180.3	375	-60000	36250	8.9	3
1371.46	9	BVNBSQFLR	Her2/neu.528.B1B4	177.4	80	37.5	58	9.9	5
1371.47	9	BVNBSQFLK	Her2/neu.528.B1B4K9	34.4	22.2	60	4264.7	14.5	4
1371.48	9	VVFGILIKK	Her2/neu.669.K9	21.6	19.4	3750	10000	34.8	3
1371.49	9	VVRENTSPK	Her2/neu.754.V2	68.8	333.3	750	1208.3	3478.3	2
1371.5	9	VVRENTSPR	Her2/neu.754.V2R9	200	5454.5	375	126.1	177.8	4
1371.52	9	LVDHVRENK	Her2/neu.806.V2K9	297.3	722.9	-60000	-58000	2580.6	1
1371.53	9	LVARNVLVK	Her2/neu.846.V2	42.3	214.3	9000	-58000	205.1	3
1371.54	9	LVARNVLVR	Her2/neu.846.V2R9	261.9	3157.9	9000	19333.3	26.7	2
1371.55	9	LVKSPNHVR	Her2/neu.852.R9	7857.1	12000	197.8	107.4	50	3
1371.56	9	KVTDFGLAR	Her2/neu.860.V2	200.7	75.9	105.9	-58000	133.3	4
1371.57	9	KVTDFGLAK	Her2/neu.860.V2K9	36.7	46.2	3461.5	-58000	816.3	2
1371.58	9	MVLESILRR	Her2/neu.889.V2	215.7	272.7	206.9	152.6	22.2	5
1371.59	9	MVLESILRK	Her2/neu.889.V2K9	61.1	16.2	20000	2636.4	381	3
1371.6	10	LVSEFSRMAK	Her2/neu.972.K10	250	71.4	2250	5272.7	61.5	3
1371.61	10	AVPLDSTFYR	Her2/neu.997.V2	-110000	88.2	30000	2636.4	72.7	2
1371.62	10	AVPLDSTFYK	Her2/neu.997.V2K10	550	33.3	1500	22307.7	228.6	2

Table XXIIC A02 Analog Peptides

Peptide	AA	Sequence	Source	A*0201 nM	A*0202 nM	A*0203 nM	A*0206 nM	A*6802 nM	A2 XRN
1382.01	9	ATCRWGLLV	Her2/neu.5.T2V9	-50000	21500	4347.8	-37000	40000	0
1382.02	9	AVCRWGLLV	Her2/neu.5.V2V9	-50000	6142.9	2631.6	18500	26666.7	0
1382.03	9	ATBRWGLLV	Her2/neu.5.T2B3V9	16666.7	215	322.6	2176.5	1739.1	2
1382.04	9	AVBRWGLLV	Her2/neu.5.V2B3V9	10000	215	140.8	2176.5	4705.9	2
1390.01	9	ALBRWGLLL	Her2/neu.5.B3	238.1	0.6	11.6	6166.7	7272.7	3

Table XXIID A24 Analog Peptides

Peptide	AA	Sequence	Source	A*2401 nM
52.0045	8	RWGLLLAL	Her2/neu.8	480
52.0056	8	SYMPIWKF	Her2/neu.609	37.5
52.0148	11	TYLPTNASLSF	Her2/neu.63	1.3
52.0159	11	PYVSRLLGICL	Her2/neu.780	375
52.0162	11	VWSYGVTVWEL	Her2/neu.905	130.4
52.0163	11	VYMIMVKCWMI	Her2/neu.951	6.7
57.0046	9	RYGLLLALF	Her2/neu.8.Y2F9	1.3
57.0047	9	TYLPTNASF	Her2/neu.63.F9	44.4
57.0048	9	CYGLGMEHF	Her2/neu.342.F9	164.4
57.0049	9	AYPDSLPDF	Her2/neu.414.Y2F9	23.5
57.005	9	AYSLTLQGF	Her2/neu.440.F9	52.2
57.0051	9	EYVNARHCF	Her2/neu.553.F9	150
57.0052	9	PYVSRLLGF	Her2/neu.780.F9	9.2
57.0053	9	KYMALESIF	Her2/neu.887.Y2F9	19
57.0054	9	RYTHQSDVF	Her2/neu.898.Y2F9	60
57.0055	9	VYSYGVTVF	Her2/neu.905.Y2F9	16.2
57.0056	9	SYGVTVWEF	Her2/neu.907.F9	26.1
57.0057	9	VYMIMVKCF	Her2/neu.951.F9	19
57.0058	9	RYRELVSEF	Her2/neu.968.Y2	36.4
57.0059	9	RYARDPQRF	Her2/neu.978.Y2	120
57.008	10	LYISAWPDSF	Her2/neu.410.F10	10
57.0082	10	GYSYLEDVRF	Her2/neu.832.Y2F10	235.3

Table XXIIE B07 Analog Peptides

Peptide	AA	Sequence	Source	B*0702 nM	B*3501 nM	B*5101 nM	B*5301 nM	B*5401 nM	B7 XRN
48.0027	8	FPKANKEI	HER2/neu.760F 118	0.16	-36000	2500	-93000	3125	1

Table XXIII. Immunogenicity A2 peptides

Source	Sequence	A*0201 nM	A*0202 nM	A*0203 nM	A*0206 nM	A*6802 nM	No. A2 Alleles Crossbound	CTL Peptide [1]	CTL Wild-type [1]	CTL Tumor [1]
Her2/neu.5	ALCRWGLLL	100	-- [3]	278	--	--	2		2/2	2/2
Her2/neu.48	HLYQGCQVV	139	307	13	514	1143	3		1/2	0/2
Her2/neu.106	QLFEDNYAL	17	226	11	463	2105	4		0/2	0/2
Her2/neu.106	QLFEDNYALA	357	662	9.1	218	74	4		0/2	0/2
Her2/neu.369	KIFGSLAFL	36	9.0	19	23	3333	4		6/7	4/7
Her2/neu.435	ILHNGAYSL	75	358	100	569	--	3		3/3	1/3
Her2/neu.653	SIISAVVGI	69	524	35	285	148	4		0/3	
Her2/neu.773	VMAGVGSPYV	200	391	13	3700	--	3		1/2	0/2
Her2/neu.789	CLTSTVQLV	208	457	6.7	308	8000	4		1/4	0/4
Her2/neu.952	YMIMVKCWMI	20	307	83	116	267	5		0/1	0/1
Her2/neu.5	ALCRWGLLL	100	-- [2]	278	--	--	2		2/2	2/2
Her2/neu.5B3V9	ALBRWGLLV	18	33	4.2	285	--	4	2/3	nt	0/3
Her2/neu.5M2V9	AMCRWGLLV	179	7167	63	128	--	3	1/2	nt	0/2
Her2/neu369	KIFGSLAFL	36.0	9	19	23.0	3333	4	10/11		7/11
Her2/neu.369L2V9	KLFGSLAFV	5.8	7.5	19	17.0	1269	4	4/4	3/4	2/4
Her2/neu.369V2V9	KVFGSLAFV	20.0	19	769	15.0	29	4	4/4	3/4	2/4
Her2/neu369T2V9	KTFGSLAFV	35.0	13	1010	14.0	17	4	nt	nt	nt
Her2/neu.665	VVLGVVFGI	14.0	--	2500	430.0	2000	2	see Table XXVII		
Her2/neu.665L2V9	VLLGVVFGV	2.4	17	14	6.0	8000	4	4/4	2/4	0/4
Her2/neu.952	YMIMVKCWMI	20	307	83	116	267	5		0/1	0/1
Her2/neu.952L2B7V10	YLIMVKBWMV	7.2	66	77	11	851	4	3/3	nt	0/3

1) Number of donors yielding a positive response/total tested.
2) -- indicates binding affinity =10,000nM.

Table XXIV. MHC-peptide binding assays: cell lines and radiolabeled ligands.

A. Class I binding assays

Species	Antigen	Allele	Cell line	Radiolabeled peptide	
				Source	Sequence
Human	A1	A*0101	Steinlin	Hu. J chain 102-110	YTAVVPLVY
	A2	A*0201	JY	HBVc 18-27 F6->Y	FLPSDYFPSV
	A2	A*0202	P815 (transfected)	HBVc 18-27 F6->Y	FLPSDYFPSV
	A2	A*0203	FUN	HBVc 18-27 F6->Y	FLPSDYFPSV
	A2	A*0206	CLA	HBVc 18-27 F6->Y	FLPSDYFPSV
	A2	A*0207	721.221 (transfected)	HBVc 18-27 F6->Y	FLPSDYFPSV
	A3		GM3107	non-natural (A3CON1)	KVFPYALINK
	A11		BVR	non-natural (A3CON1)	KVFPYALINK
	A24	A*2402	KAS116	non-natural (A24CON1)	AYIDNYNKF
	A31	A*3101	SPACH	non-natural (A3CON1)	KVFPYALINK
	A33	A*3301	LWAGS	non-natural (A3CON1)	KVFPYALINK
	A28/68	A*6801	C1R	HBVc 141-151 T7->Y	STLPETYVVRR
	A28/68	A*6802	AMAI	HBV pol 646-654 C4->A	FTQAGYPAL
	B7	B*0702	GM3107	A2 sigal seq. 5-13 (L7->Y)	APRTLVYLL
	B8	B*0801	Steinlin	HIVgp 586-593 Y1->F, Q5->Y	FLKDYQLL
	B27	B*2705	LG2	R 60s	FRYNGLIHR
	B35	B*3501	C1R, BVR	non-natural (B35CON2)	FPFKYAAAF
	B35	B*3502	TISI	non-natural (B35CON2)	FPFKYAAAF
	B35	B*3503	EHM	non-natural (B35CON2)	FPFKYAAAF
	B44	B*4403	PITOUT	EF-1 G6->Y	AEMGKYSFY
	B51		KAS116	non-natural (B35CON2)	FPFKYAAAF
	B53	B*5301	AMAI	non-natural (B35CON2)	FPFKYAAAF
	B54	B*5401	KT3	non-natural (B35CON2)	FPFKYAAAF
	Cw4	Cw*0401	C1R	non-natural (C4CON1)	QYDDAVYKL
	Cw6	Cw*0602	721.221 transfected	non-natural (C6CON1)	YRHDGGNVL
	Cw7	Cw*0702	721.221 transfected	non-natural (C6CON1)	YRHDGGNVL
Mouse	D^b		EL4	Adenovirus E1A P7->Y	SGPSNTYPEI
	K^b		EL4	VSV NP 52-59	RGYVFQGL
	D^d		P815	HIV-IIIB ENV G4->Y	RGPYRAFVTI
	K^d		P815	non-natural (KdCON1)	KFNPMKTYI
	L^d		P815	HBVs 28-39	IPQSLDSYWTSL

B. Class II binding assays

Species	Antigen	Allele	Cell line	Radiolabeled peptide	
				Source	Sequence
Human	DR1	DRB1*0101	LG2	HA Y307-319	YPKYVKQNTLKLAT
	DR2	DRB1*1501	L466.1	MBP 88-102Y	VVHFFKNIVTPRTPPY
	DR2	DRB1*1601	L242.5	non-natural (760.16)	YAAFAAAKTAAAFA
	DR3	DRB1*0301	MAT	MT 65kD Y3-13	YKTIAFDEEARR
	DR4w4	DRB1*0401	Preiss	non-natural (717.01)	YARFQSQTTLKQKT
	DR4w10	DRB1*0402	YAR	non-natural (717.10)	YARFQRQTTLKAAA
	DR4w14	DRB1*0404	BIN 40	non-natural (717.01)	YARFQSQTTLKQKT
	DR4w15	DRB1*0405	KT3	non-natural (717.01)	YARFQSQTTLKQKT
	DR7	DRB1*0701	Pitout	Tet. tox. 830-843	QYIKANSKFIGITE
	DR8	DRB1*0802	OLL	Tet. tox. 830-843	QYIKANSKFIGITE
	DR8	DRB1*0803	LUY	Tet. tox. 830-843	QYIKANSKFIGITE
	DR9	DRB1*0901	HID	Tet. tox. 830-843	QYIKANSKFIGITE
	DR11	DRB1*1101	Sweig	Tet. tox. 830-843	QYIKANSKFIGITE
	DR12	DRB1*1201	Herluf	unknown eluted peptide	EALIHQLKINPYVLS
	DR13	DRB1*1302	H0301	Tet. tox. 830-843 S->A	QYIKANAKFIGITE
	DR51	DRB5*0101	GM3107 or L416.3	Tet. tox. 830-843	QYIKANAKFIGITE
	DR51	DRB5*0201	L255.1	HA 307-319	PKYVKQNTLKLAT
	DR52	DRB3*0101	MAT	Tet. tox. 830-843	NGQIGNDPNRDIL
	DR53	DRB4*0101	L257.6	non-natural (717.01)	YARFQSQTTLKQKT
	DQ3.1	A1*0301/DQB1*0	PF	non-natural (ROIV)	YAHAAHAAHAAHAAHAA
Mouse	IA^b		DB27.4	non-natural (ROIV)	YAHAAHAAHAAHAAHAA
	IA^d		A20	non-natural (ROIV)	YAHAAHAAHAAHAAHAA
	IA^k		CH-12	HEL 46-61	YNTDGSTDYGILQINSR
	IA^s		LS102.9	non-natural (ROIV)	YAHAAHAAHAAHAAHAA
	IA^u		91.7	non-natural (ROIV)	YAHAAHAAHAAHAAHAA
	IE^d		A20	Lambda repressor 12-26	YLEDARRKKAIYEKKK
	IE^k		CH-12	Lambda repressor 12-26	YLEDARRKKAIYEKKK

Table XXV. Antibodies used in MHC purification.

Monoclonal antibody	Specificity
W6/32	HLA-class I
B123.2	HLA-B and C
IVD12	HLA-DQ
LB3.1	HLA-DR
M1/42	H-2 class I
28-14-8S	H-2 Db and Ld
34-5-8S	H-2 Dd
B8-24-3	H-2 Kb
SF1-1.1.1	H-2 Kd
Y-3	H-2 Kb
10.3.6	H-2 IAk
14.4.4	H-2 IEd, IEK
MKD6	H-2 IAd
Y3JP	H-2 IAb, IAs, IAu

Table XXVI. Crossbinding data of A2 supermotif peptides

Source	AA	Sequence	A*0201 nM	A*0202 nM	A*0203 nM	A*0206 nM	A*6802 nM	No. A2 Alleles Crossbound
Her2/neu.5	9	ALCRWGLLL	100	--	278	--	--	2
Her2/neu.5	10	ALCRWGLLLA	139	1955	12	1947	2500	2
Her2/neu.48	9	HLYQGCQVV	139	307	13	514	1143	3
Her2/neu.106	9	QLFEDNYAL	17	226	11	463	2105	4
Her2/neu.106	10	QLFEDNYALA	357	662	9.1	218	74	4
Her2/neu.144	10	SLTEILKGGV	238	--	22	--	--	2
Her2/neu.153	9	VLIQRNPQL	23	3909	3.3	1057	--	2
Her2/neu.369	9	KIFGSLAFL	36	9.0	19	23	3333	4
Her2/neu.435	9	ILHNGAYSL	75	358	100	569	--	3
Her2/neu.466	9	ALIHHNTHL	278	1265	10	1762	--	2
Her2/neu.508	9	GLACHQLCA	417	--	127	--	9091	2
Her2/neu.653	9	SIISAVVGI	69	524	35	285	148	4
Her2/neu.665	9	VVLGVVFGI	14	--	2500	430	2000	2
Her2/neu.689	9	RLLQETELV	21	--	625	34	--	2
Her2/neu.767	9	ILDEAYVMA	238	--	4167	3083	--	1
Her2/neu.773	10	VMAGVGSPYV	200	391	13	3700	--	3
Her2/neu.789	9	CLTSTVQLV	208	457	6.7	308	8000	4
Her2/neu.799	9	QLMPYGCLL	217	977	114	712	--	2
Her2/neu.952	10	YMIMVKCWMI	20	307	83	116	267	5
Her2/neu.952	9	YMIMVKCWM	217	--	625	2643	1000	1

-- indicates binding affinity =10,000nM.

Table XXVII. Immunogenicity of A2 supermotif peptides

Source	AA	Sequence	A*0201 nM	A*0202 nM	A*0203 nM	A*0206 nM	A*6802 nM	No. A2 Alleles Crossbound	CTL Wild-type [1]	CTL Tumor [1]	CTL Wild-type [2]	CTL Tumor [2]
Her2/neu.5	9	ALCRWGLLL	100	-- [3]	278	--	--	2	2/2	2/2		
Her2/neu.48	9	HLYQGCQVV	139	307	13	514	1143	3	1/2	0/2	2/2	1/2
Her2/neu.106	9	QLFEDNYAL	17	226	11	463	2105	4	0/2	0/2		
Her2/neu.106	10	QLFEDNYALA	357	662	9.1	218	74	4	0/2	0/2		
Her2/neu.369	9	KIFGSLAFL	36	9.0	19	23	3333	4	6/7	4/7	2/2	2/2
Her2/neu.435	9	ILHNGAYSL	75	358	100	569	--	3	3/3	1/3	2/2	2/2
Her2/neu.653	9	SIISAVVGI	69	524	35	285	148	4	0/3			
Her2/neu.665	9	VVLGVVFGI	14	--	2500	430	2000	2			2/2	2/2
Her2/neu.773	10	VMAGVGSPYV	200	391	13	3700	--	3	1/2	0/2	1/2	1/2
Her2/neu.789	9	CLTSTVQLV	208	457	6.7	308	8000	4	1/4	0/4	1/2	
Her2/neu.952	10	YMIMVKCWMI	20	307	83	116	267	5	0/1	0/1	2/2	2/2

1) Number of donors yielding a positive response/total tested.
2) Data from ovarian cancer patients.
3) -- indicates binding affinity =10,000nM.

Table XXVIII. Immunogenicity A2 supermotif analog peptides

Source	Sequence	A*0201 nM	A*0202 nM	A*0203 nM	A*0206 nM	A*6802 nM	No. A2 Alleles Crossbound	CTL Peptide [1]	CTL Wild-type [1]	CTL Tumor [1]
Her2/neu.5	ALCRWGLLL	100	-- [2]	278	--	--	2		2/2	2/2
Her2/neu.5B3V9	ALBRWGLLV	18	33	4.2	285	--	4	2/3	nt	0/3
Her2/neu.5M2V9	AMCRWGLLV	179	7167	63	128	--	3	1/2	nt	0/2
Her2/neu369	KIFGSLAFL	36.0	9	19	23.0	3333	4	10/11		7/11
Her2/neu.369L2V9	KLFGSLAFV	5.8	7.5	19	17.0	1269	4	4/4	3/4	2/4
Her2/neu.369V2V9	KVFGSLAFV	20.0	19	769	15.0	29	4	4/4	3/4	2/4
Her2/neu369T2V9	KTFGSLAFV	35.0	13	1010	14.0	17	4	nt	nt	nt
Her2/neu.665	VVLGVVFGI	14.0	--	2500	430.0	2000	2			
Her2/neu.665L2V9	VLLGVVFGV	2.4	17	14	6.0	8000	4	4/4	2/4	0/4
Her2/neu.952	YMIMVKCWMI	20	307	83	116	267	5		0/1	0/1
Her2/neu.952L2B7V10	YLIMVKBWMV	7.2	66	77	11	851	4	3/3	nt	0/3

1) Number of donors yielding a positive response/total tested.
2) -- indicates binding affinity =10,000nM.

Table XXIX. Her2/neu DR supertype primary binding

Peptide	DR147 Algo Sum	Sequence	Source	DR1 nM	DR4w4 nM	DR7 nM	DR147 Cross-binding
39.0241	2	LCRWGLLLALLPPGA	Her2/neu.6	53	--	--	1
39.0242	2	RWGLLLALLPPGAAS	Her2/neu.8	0.42	161	--	2
39.0243	2	WGLLLALLPPGAAST	Her2/neu.9	0.98	35	--	2
39.0244	2	GTDMKLRLPASPETH	Her2/neu.28	5000	--	--	0
39.0245	2	DMKLRLPASPETHLD	Her2/neu.30	5000	--	--	0
39.0246	2	NLELTYLPTNASLSF	Her2/neu.59	11	118	368	3
39.0247	3	LTYLPTNASLSFLQD	Her2/neu.62	10	136	78	3
39.0248	2	TQLFEDNYALAVLDN	Her2/neu.105	94	--	1563	1
39.0249	2	VCPLHNQEVTAEDGT	Her2/neu.314	--	--	--	0
39.0250	2	CKKIFGSLAFLPESF	Her2/neu.367	21	--	926	2
39.0251	2	LSVFQNLQVIRGRIL	Her2/neu.422	28	672	86	3
39.0252	2	LRELGSGLALIHHNT	Her2/neu.458	161	--	--	1
39.0253	3	KPDLSYMPIWKFPDE	Her2/neu.605	152	--	8621	1
39.0254	3	ASPLTSIISAVVGIL	Her2/neu.648	56	--	714	2
39.0255	2	LTSIISAVVGILLVV	Her2/neu.651	26	--	5102	1
39.0256	3	VVGILLVVVLGVVFG	Her2/neu.658	--	--	--	0
39.0257	3	LLVVVLGVVFGILIK	Her2/neu.662	>6250	--	--	0
39.0258	2	VLGVVFGILIKRRQQ	Her2/neu.666	71	--	781	2
39.0259	2	ETELVEPLTPSGAMP	Her2/neu.693	833	--	--	1
39.0260	2	VEPLTPSGAMPNQAQ	Her2/neu.697	>6250	--	--	0
39.0261	2	ETELRKVKVLGSGAF	Her2/neu.717	313	1286	658	2
39.0262	2	GENVKIPVAIKVLRE	Her2/neu.743	79	--	807	2
39.0263	2	IKVLRENTSPKANKE	Her2/neu.752	--	--	--	0
39.0264	3	KEILDEAYVMAGVGS	Her2/neu.765	--	6164	--	0
39.0265	3	DEAYVMAGVGSPYVS	Her2/neu.769	100	196	125	3
39.0266	2	SRLLGICLTSTVQLV	Her2/neu.783	14	375	45	3
39.0267	2	TVQLVTQLMPYGCLL	Her2/neu.793	22	978	2500	2
39.0268	3	LLNWCMQIAKGMSYL	Her2/neu.822	6.0	--	208	2
39.0269	2	ITDFGLARLLDIDET	Her2/neu.861	1042	--	--	0
39.0270	3	KVPIKWMALESILRR	Her2/neu.883	2.3	652	1316	2
39.0271	3	PIKWMALESILRRRF	Her2/neu.885	6.3	1286	3205	1
39.0272	2	IKWMALESILRRRFT	Her2/neu.886	5.3	1125	6250	1
39.0273	2	GVTVWELMTFGAKPY	Her2/neu.909	3.6	1364	1471	1
39.0274	3	VWELMTFGAKPYDGI	Her2/neu.912	58	818	676	3
39.0275	2	GERLPQPPICTIDVY	Her2/neu.938	--	--	--	0
39.0276	2	QPPICTIDVYMIMVK	Her2/neu.943	75	7500	250	2
39.0277	2	DVYMIMVKCWMIDSE	Her2/neu.950	179	790	192	3
39.0278	2	QGFFCPDPAPGAGGM	Her2/neu.1028	--	1957	--	0
39.0279	3	TDGYVAPLTCSPQPE	Her2/neu.1124	--	--	--	0
39.0280	2	QPDVRPQPPSPREGP	Her2/neu.1142	7143	--	--	0
39.0281	2	PSTFKGTPTAENPEY	Her2/neu.1234	--	--	--	0

-- indicates binding affinity =10,000nM.

Table XXX. DR supertype crossbinding

Peptide	Sequence	Source	DR1 nM	DR4w4 nM	DR7 nM	DR2w2 ß1 nM	DR2w2 ß2 nM	DR6w1 9 nM	DR5w1 1 nM	DR8w2 nM	DR147 Binding	Broad Binding (5/8)
39.0242	RWGLLLALLPPGAAS	Her2/neu.8	0.40	161	--	70	741	--	282	408	2	6
39.0243	WGLLLALLPPGAAST	Her2/neu.9	1.0	35	--	43	1818	--	80	109	2	5
39.0246	NLELTYLPTNASLSF	Her2/neu.59	11	118	368	325	2222	2059	4000	2227	3	4
39.0247	LTYLPTNASLSFLQD	Her2/neu.62	10	136	78	910	357	125	4878	9074	3	6
39.0250	CKKIFGSLAFLPESF	Her2/neu.367	21	--	926	1300	--	1029	--	--	2	2
39.0251	LSVFQNLQVIRGRIL	Her2/neu.422	28	672	86	325	270	614	2000	1485	3	6
39.0254	ASPLTSIISAVVGIL	Her2/neu.648	56	--	714	96	5405	73	--	--	2	4
39.0258	VLGVVFGILIKRRQQ	Her2/neu.666	71	--	781	827	323	233	43	77	2	7
39.0261	ETELRKVKVLGSGAF	Her2/neu.717	313	1286	658	4790	3846	2500	3279	1960	2	2
39.0262	GENVKIPVAIKVLRE	Her2/neu.743	79	--	807	1936	5882	8750	--	--	2	2
39.0265	DEAYVMAGVGSPYVS	Her2/neu.769	100	196	125	3138	833	1750	7407	860	3	5
39.0266	SRLLGICLTSTVQLV	Her2/neu.783	14	375	45	414	--	10	1429	--	3	5
39.0267	TVQLVTQLMPYGCLL	Her2/neu.793	22	978	2500	12	--	1129	--	7101	2	3
39.0268	LLNWCMQIAKGMSYL	Her2/neu.822	6.0	--	208	1597	17	90	50	120	2	6
39.0270	KVPIKWMALESILRR	Her2/neu.883	2.3	652	1316	3.4	9.5	1129	2740	6203	2	4
39.0274	VWELMTFGAKPYDGI	Her2/neu.912	58	818	676	92	200	8750	3704	5506	3	5
39.0276	QPPICTIDVYMIMVK	Her2/neu.943	75	7500	250	169	7407	2692	4348	9608	2	3
39.0277	DVYMIMVKCWMIDSE	Her2/neu.950	179	790	192	1936	4762	--	909	1089	3	4

-- indicates binding affinity =10,000nM.

Table XXXI. DR3 binding

Peptide	Sequence	Source	DR3 nM
39.0338	RLPASPETHLDMLRH	Her2/neu.34	--
39.0339	SLSFLQDIQEVQGYV	Her2/neu.70	5769
39.0340	VLIAHNQVRQVPLQR	Her2/neu.84	--
39.0341	GTQLFEDNYALAVLD	Her2/neu.104	1364
39.0342	DTILWKDIFHKNNQL	Her2/neu.165	--
39.0343	ALTLIDTNRSRACHP	Her2/neu.180	8571
39.0344	KGPLPTDCCHEQCAA	Her2/neu.228	--
39.0345	LVTYNTDTFESMPNP	Her2/neu.271	--
39.0346	YNYLSTDVGSCTLVC	Her2/neu.301	--
39.0347	NQEVTAEDGTQRCEK	Her2/neu.319	--
39.0348	CYGLGMEHLREVRAV	Her2/neu.342	--
39.0349	SLAFLPESFDGDPAS	Her2/neu.373	--
39.0350	PESFDGDPASNTAPL	Her2/neu.378	--
39.0351	TAPLQPEQLQVFETL	Her2/neu.389	--
39.0352	LALIHHNTHLCFVHT	Her2/neu.465	968
39.0353	VHTVPWDQLFRNPHQ	Her2/neu.477	--
39.0354	WDQLFRNPHQALLHT	Her2/neu.482	333
39.0355	LQGLPREYVNARHCL	Her2/neu.547	--
39.0356	VTCFGPEADQCVACA	Her2/neu.574	--
39.0357	PSGVKPDLSYMPIWK	Her2/neu.601	--
39.0358	IWKFPDEEGACQPCP	Her2/neu.613	--
39.0359	HSCVDLDDKGCPAEQ	Her2/neu.632	--
39.0360	MRRLLQETELVEPLT	Her2/neu.687	--
39.0361	QMRILKETELRKVKV	Her2/neu.711	938
39.0362	AIKVLRENTSPKANK	Her2/neu.751	--
39.0363	NKEILDEAYVMAGVG	Her2/neu.764	--
39.0364	GMSYLEDVRLVHRDL	Her2/neu.832	1667
39.0365	VRLVHRDLAARNVLV	Her2/neu.839	882
39.0366	ARLLDIDETEYHADG	Her2/neu.867	968
39.0367	ETEYHADGGKVPIKW	Her2/neu.874	--
39.0368	IKWMALESILRRRFT	Her2/neu.886	682
39.0369	CWMIDSECRPRFREL	Her2/neu.958	667
39.0370	FRELVSEFSRMARDP	Her2/neu.969	4225
39.0371	FSRMARDPQRFVVIQ	Her2/neu.976	1875
39.0372	FVVIQNEDLGPASPL	Her2/neu.986	--
39.0373	YRSLLEDDDMGDLVD	Her2/neu.100	4762
39.0374	RSLLEDDDMGDLVDA	Her2/neu.100	--
39.0375	GDLVDAEEYLVPQQG	Her2/neu.101	--
39.0376	QGFFCPDPAPGAGGM	Her2/neu.102	--
39.0377	DLTLGLEPSEEEAPR	Her2/neu.105	--
39.0378	SDVFDGDLGMGAAKG	Her2/neu.108	--
39.0379	LQRYSEDPTVPLPSE	Her2/neu.110	--
39.0380	TVPLPSETDGYVAPL	Her2/neu.111	--
39.0381	KNGVVKDVFAFGGAV	Her2/neu.117	--
39.0382	QGGAAPQPHPPPAFS	Her2/neu.120	--
39.0383	DNLYYWDQDPPERGA	Her2/neu.121	--

-- indicates binding affinity =10,000nM.

Table XXXII. HTL candidates

Peptide	Sequence	Motif	Source	DR1 nM	DR4w4 nM	DR7 nM	DR3 nM	DR2w2 ß1 nM	DR2w2 ß2 nM	DR6w1 9 nM	DR5w1 1 nM	DR8w2 nM	DR147 Degen	Broad Degen (5/8)	DR3 Binder
39.0242	RWGLLLALLPPGAAS	DR sup	Her2/neu.8	0.40	161	--	--	70	741	--	282	408	2	6	0
39.0243	WGLLLALLPPGAAST	DR sup	Her2/neu.9	1.0	35	--	--	43	1818	--	80	109	2	5	0
39.0247	LTYLPTNASLSFLQD	DR sup	Her2/neu.62	10	136	78	--	910	357	125	4878	9074	3	6	0
39.0251	LSVFQNLQVIRGRIL	DR sup	Her2/neu.422	28	672	86	--	325	270	614	2000	1485	3	6	0
39.0352	LALIHHNTHLCFVHT	DR3	Her2/neu.465	357	>8182	1250	968	92	--	4.7	8000	1485	1	3	1
39.0354	WDQLFRNPHQALLHT	DR3	Her2/neu.482	--	>8182	--	333	6067	--	85	--	--	0	1	1
39.0258	VLGVVFGILIKRRQQ	DR sup	Her2/neu.666	71	--	781	--	827	323	233	43	77	2	7	0
39.0361	QMRILKETELRKVKV	DR3	Her2/neu.711	119	>8182	1923	938	607	34	4375	4878	7656	1	3	1
39.0265	DEAYVMAGVGSPYVS	DR sup	Her2/neu.769	100	196	125	--	3138	833	1750	7407	860	3	5	0
39.0266	SRLLGICLTSTVQLV	DR sup	Her2/neu.783	14	375	45	--	414	--	10	1429	--	3	5	0
39.0268	LLNWCMQIAKGMSYL	DR sup	Her2/neu.822	6.0	--	208	--	1597	17	90	50	120	2	6	0
39.0365	VRLVHRDLAARNVLV	DR3	Her2/neu.839	147	3058	1087	882	1422	6061	81	74	490	1	4	1
39.0366	ARLLDIDETEYHADG	DR3	Her2/neu.867	--	>8182	--	968	--	--	--	--	--	0	0	1
39.0270	KVPIKWMALESILRR	DR sup	Her2/neu.883	2.3	652	1316	4839	3.4	9.5	1129	2740	6203	2	4	0
39.0368	IKWMALESILRRRFT	DR3	Her2/neu.886	17	3224	4098	682	11	2.5	2500	370	731	1	5	1
39.0274	VWELMTFGAKPYDGI	DR sup	Her2/neu.912	58	818	676	--	92	200	8750	3704	5506	3	5	0
39.0369	CWMIDSECRPRFREL	DR3	Her2/neu.958	1389	>8182	--	667	--	1333	--	--	--	0	0	1

-- indicates binding affinity =10,000nM.

WHAT IS CLAIMED IS

1. A peptide composition of less than 500 amino acid residues comprising a peptide epitope useful for inducing an immune response against HER2/neu said epitope (a) having an amino acid sequence of about 8 to about 13 amino acid residues that have at least 65% identity with a native amino acid sequence of HER2/neu and, (b) binding to at least one HLA class I allele with an IC_{50} of less than about 500 nM.

2. The composition of claim 1, further wherein said peptide has at least 77% identity with a native HER2/neu amino acid sequence.

3. The composition of claim 1, further wherein said peptide has 100% identity with a native HER2/neu amino acid sequence.

4. A pharmaceutical composition comprising a peptide and a pharmaceutical carrier, wherein the peptide is a peptide of Table VII (A1 supermotif), Table VIII (A2 supermotif/A*0201 motif), Table IX (A3 supermotif), Table X (A24 supermotif), Table XI (B7 supermotif), Table XII (B27 supermotif), Table XIII (B58 supermotif), Table XIV (B62 supermotif), Table XV (A1 motif), Table XVI (A3 motif), Table XVII (A11 motif), or Table XVIII (A24 motif) comprising an IC_{50} of less than about 500 nM for at least one HLA class I molecule.

5. The pharmaceutical composition of claim 4 wherein the composition comprises the peptide in a form of nucleic acids that encode the peptide.

6. The pharmaceutical composition of claim 5 wherein the composition comprises the peptide in a form of nucleic acids that encode the epitope and one or more additional peptide(s).

7. The composition of claim 4, wherein the peptide is comprised by a longer peptide, with a *proviso* that the longer peptide is not an entire native antigen.

8. The pharmaceutical composition of claim 4 wherein the peptide is in a human dose form, and the carrier is in a human unit dose.

9. A peptide composition of claim 1 comprising an analog of a peptide epitope, wherein the peptide epitope is an epitope of Table VII (A1 supermotif), Table VIII (A2 supermotif/A2.1 motif), Table IX (A3 supermotif), Table X (A24 supermotif), Table XI (B7 supermotif), Table XII (B27 supermotif), Table XIII (B58 supermotif), Table XIV (B62 supermotif), Table XV (A1 motif), Table XVI (A3 motif), Table XVII (A11 motif), or Table XVIII (A24 motif), said analog comprising a preferred or less preferred amino acid of Table II substituted in for a starting residue, or having a deleterious residue of Table II substituted out of the starting sequence and replaced by a non-deleterious residue.

10. A peptide composition of claim 9 comprising a peptide of Table XXII.

11. A method for inducing a cytotoxic T lymphocyte response, said method comprising steps of:

providing a peptide that comprises an IC_{50} of less than about 500 nM for an HLA class I molecule, wherein the peptide is a peptide of Table VII (A1 supermotif), Table VIII (A2 supermotif/A2.1 motif), Table IX (A3 supermotif), Table X (A24 supermotif), Table XI (B7 supermotif), Table XII (B27 supermotif), Table XIII (B58 supermotif), Table XIV (B62 supermotif), Table XV (A1 motif), Table XVI (A3 motif), Table XVII (A11 motif), Table XVIII (A24 motif), or Table XXII; and,

administering said peptide to a human.

12. The method of claim 11, wherein the providing step provides the peptide in a form of nucleic acids that encode the peptide.

13. The method of claim 12, wherein the providing step provides the peptide in a form of nucleic acids that encode the peptide and at least one additional peptide, with a *proviso* that an additional peptide is not an entire native antigen.

14. The method of claim 11, wherein the providing step provides the peptide comprised by a longer peptide, with a *proviso* that the longer peptide is not an entire native antigen.

15. A method for inducing a cytotoxic T lymphocyte response, said method comprising steps of:

providing a pharamceutical composition comprising a peptide and a pharmaceutical carrier, wherein the peptide induces a cytotoxic T cell response *in vitro* and/or *in vivo*, and further wherein the peptide is a peptide of Table VII (A1 supermotif), Table VIII (A2 supermotif/A2.1 motif), Table IX (A3 supermotif), Table X (A24 supermotif), Table XI (B7 supermotif), Table XII (B27 supermotif), Table XIII (B58 supermotif), Table XIV (B62 supermotif), Table XV (A1 motif), Table XVI (A3 motif), Table XVII (A11 motif), Table XVIII (A24 motif), Table XXII, or Table XXIII; and,

administering said pharmaceutical composition to a human.

16. The method of claim 15, wherein the providing step provides the peptide in a form of nucleic acids that encode the peptide.

17. The method of claim 16, wherein the providing step provides the peptide in a form of nucleic acids that encode the peptide and at least one additional peptide, with a *proviso* that an additional peptide is not an entire native antigen.

18. The method of claim 15, wherein the providing step provides the peptide comprised by a longer peptide, with a *proviso* that the longer peptide is not an entire native antigen.

19. The method of claim 15, wherein the providing step comprises a peptide that induces a cytotoxic T cell response when complexed with an HLA class I molecule and is presented to an HLA class I-restricted cytotoxic T cell.

20. A peptide composition of less than 500 amino acid residues comprising a peptide epitope useful for inducing an immune response against HER2/neu said epitope (a) having an amino acid sequence of about 6 to about 25 amino acid residues that have at least 65% identity with a native amino acid sequence of HER2/neu and, (b) binding to at least one HLA class II HLA allele with an IC_{50} of less than about 1000 nM.

21. The peptide composition of claim 20, further wherein said peptide has at least 77% identity with a native HER2/neu amino acid sequence.

22. The peptide composition of claim 20, further wherein said peptide has 100% identity with a native HER2/neu amino acid sequence.

23. A pharmaceutical composition comprising:

a human dose form of a peptide of Table XIX or Table XX that comprises an IC_{50} of less than about 1,000 nM for at least one HLA DR molecule of an HLA DR supertype; and,

a human dose of a pharmaceutically acceptable carrier.

24. The pharmaceutical composition of claim 23 wherein the composition comprises the peptide in a form of nucleic acids that encode the peptide.

25. The pharmaceutical composition of claim 24 wherein the composition comprises the peptide in a form of nucleic acids that encode the peptide and at least one additional peptide, with a *proviso* that an additional peptide is not an entire native antigen.

26. The pharmaceutical composition of claim 25, wherein the peptide is comprised by a longer peptide, with a *proviso* that the longer peptide is not an entire native antigen.

27. A peptide composition of claim 20 comprising an analog of a peptide epitope of Table XIX or Table XX, said analog comprising a preferred or less preferred amino acid of Table III substituted in for a starting residue, and/or having a deleterious residue of Table III substituted out of the starting sequence and replaced by a non-deleterious residue.

28. A method for inducing a helper T lymphocyte response, said method comprising steps of:

providing a pharmaceutical composition comprising a human dose of a peptide that comprises an IC_{50} of less than about 1,000 nM for an HLA class II molecule and a human dose of a pharmaceutical carrier, wherein the peptide is a peptide of Table XIX or Table XX; and,

administering said peptide to a human.

29. The method of claim 28, wherein the providing step provides the peptide in a form of nucleic acids that encode the peptide.

30. The method of claim 29, wherein the providing step provides the peptide in a form of nucleic acids that encode the peptide and at least one additional peptide, with a *proviso* that an additional peptide is not an entire native antigen.

31. The method of claim 28, wherein the providing step provides the peptide comprised by a longer peptide, with a *proviso* that the longer peptide is not an entire native antigen.

32. A method for inducing a helper T lymphocyte response, said method comprising steps of:

providing a pharmaceutical composition comprising a human dose of a peptide that induces a helper T cell response *in vitro* and/or *in vivo* and a pharmaceutically acceptable carrier, wherein the peptide is a peptide of Table XIX or Table XX; and,

administering said pharmaceutical composition to a human.

33. The method of claim 32, wherein the providing step provides the peptide in a form of nucleic acids that encode the peptide.

34. The method of claim 33, wherein the providing step provides the peptide in a form of nucleic acids that encode the peptide and at least one additional peptide, with a *proviso* that an additional peptide is not an entire native antigen.

35. The method of claim 32, wherein the providing step provides the peptide comprised by a longer peptide, with a *proviso* that the longer peptide is not an entire native antigen.

36. The method of claim 32, wherein the providing step comprises a peptide that induces a helper T cell response when complexed with an HLA class II molecule and is presented to an HLA class II-restricted helper T cell.

37. A vaccine for preventing or treating cancer that induces a protective or therapeutic immune response, wherein said vaccine comprises:

at least one peptide selected from Table(s) VII-XX or Table XXII; and,

a pharmaceutically acceptable carrier.

38. A kit for a vaccine that induces a protective or therapeutic immune response to a tumor, said vaccine comprising:

at least one peptide selected from Table(s) VII-XX or Table XXII;

a pharmaceutically acceptable carrier; and,

instructions for administration to a patient.

39. A method for monitoring or evaluating an immune response to a tumor or an epitope thereof in a patient having a known HLA type, the method comprising:

incubating a T lymphocyte sample from the patient with a peptide selected from Table(s) VII-XX or Table XXII, wherein that peptide bears a motif corresponding to at least one HLA allele present in said patient; and,

detecting the presence of a T lymphocyte that recognizes the peptide.

40. The method of claim 39, wherein the peptide is comprised by a tetrameric complex.

ABSTRACT OF THE DISCLOSURE

This invention uses our knowledge of the mechanisms by which antigen is recognized by T cells to identify and prepare HER2/neu epitopes, and to develop epitope-based vaccines directed towards HER2/neu-bearing tumors. More specifically, this application communicates our discovery of pharmaceutical compositions and methods of use in the prevention and treatment of cancer.

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I declare that:

My residence, post office address and citizenship are as stated below next to my name; I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: **INDUCING CELLULAR IMMUNE RESPONSES TO HER2/neu USING PEPTIDE AND NUCLEIC ACID COMPOSITIONS** the specification of which __X__ is attached hereto or ____ was filed on _____ as Application No. _____ and was amended on _____ (if applicable).

I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56. I claim foreign priority benefits under Title 35, United States Code, Section 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Country	Application No.	Date of Filing	Priority Claimed Under 35 USC 119

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below:

Application No.	Filing Date

I claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application No.	Date of Filing	Status
09/189,702	November 10, 1998	pending
08/205,713	March 4, 1994	pending
08/159,184	November 29, 1993	abandoned
08/073,205	June 4, 1993	abandoned
08/027,146	March 5, 1993	abandoned

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I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signature of Inventor 1 JOHN FIKES Date	Signature of Inventor 2 ALESSANDRO SETTE Date	Signature of Inventor 3 JOHN SIDNEY Date
Signature of Inventor 4 SCOTT SOUTHWOOD Date	Signature of Inventor 5 ROBERT CHESNUT Date	Signature of Inventor 6 ESTEBAN CELIS Date
Signature of Inventor 7 ELISSA KEOGH Date		

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